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United States Patent and Trademark Office

March 21, 2005

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APPLICATION NUMBER: *60/547,757*
FILING DATE: *February 24, 2004*
RELATED PCT APPLICATION NUMBER: *PCT/US05/06311*

Certified by

Jon W. Dudas

Under Secretary of Commerce
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PTO/SB/16 (10-01)
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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c).

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INVENTOR(S)

Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
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Nathanael	GRAY	San Diego, CA

☒ *Additional inventors are being named on the 1 separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

IMMUNOSUPPRESSANT COMPOUNDS AND COMPOSITIONS

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ENCLOSED APPLICATION PARTS *(check all that apply)*

☒ Specification *Number of Pages* 53 ☐ CD(s), Number

☐ Drawing(s) *Number of Sheets* ☒ Other (specify) Fee Transmittal ; Return Postcard

☐ Application Data Sheet. See 37 CFR 1.76

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☐ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check or money order is enclosed to cover the filing fees

FILING FEE AMOUNT ($)

☒ The Commissioner is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number: 50-1885 — 160

☐ Payment by credit card. Form PTO-2038 is attached.

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are: _____.

Respectfully submitted,

SIGNATURE Scott W. Reid

TYPED or PRINTED NAME Scott W. Reid

TELEPHONE 858-812-1796

Date 2/24/2004

REGISTRATION NO. *(if appropriate)* 48,097

Docket Number: P1152US00

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

PROVISIONAL APPLICATION COVER SHEET

Additional Page

PTO/SB/16 (02-01)
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Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Docket Number	P1152US00

INVENTOR(S)/APPLICANT(S)

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Thomas H.	MARSILJE	San Diego, CA

Number 1 of 1

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FEE TRANSMITTAL for FY 2004

Effective 10/01/2003. Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 160

Complete if Known	
Application Number	
Filing Date	24 February 2004
First Named Inventor	Shifeng PAN
Examiner Name	
Art Unit	
Attorney Docket No.	P1152US00

METHOD OF PAYMENT *(check all that apply)*

☐ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None

☒ Deposit Account:

Deposit Account Number: 50-1885

Deposit Account Name: The Genomics Institute of the Novartis Research Foundation

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FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	770	2001	385	Utility filing fee	160
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1) ($) 160

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

			Extra Claims		Fee from below		Fee Paid
Total Claims		-20 ** =	0	X		=	0
Independent Claims		-3 ** =	0	X		=	0
Multiple Dependent				X		=	0

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) 0

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet.	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing a brief in support of an appeal	
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive – unavoidable	
1453	1,330	2453	665	Petition to revive – unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17 (q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR § 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37 CFR § 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify) _____

*Reduced by Basic Filing Fee Paid **SUBTOTAL (3)** ($) 0

SUBMITTED BY				Complete *(if applicable)*	
Name (Print/Type)	Scott W. Reid	*Registration No. (Attorney/Agent)*	48,097	*Telephone*	858-812-1796
Signature				*Date*	24 February 2004

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I hereby certify that this is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above, addressed to: Mail Stop Provisional Patent Application, Commissioner for Patents PO Box 1450, Alexandria, VA 22313-1450

By: _____
Scott W. Reid

GNF Docket No: P1152US00

United States Provisional Patent Application

Immunosuppressant Compounds and Compositions

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PATENT

GNF Docket No: P1152US00

IMMUNOSUPPRESSANT COMPOUNDS AND COMPOSITIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

Not applicable.

BACKGROUND OF THE INVENTION

Field of the Invention

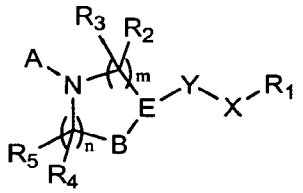
The invention provides a novel class of immunosuppressant compounds useful in the treatment or prevention of diseases or disorders mediated by lymphocyte interactions, particularly diseases associated with EDG receptor mediated signal transduction.

Background

EDG receptors belong to a family of closely related, lipid activated G-protein coupled receptors. EDG-1, EDG-3, EDG-5, EDG-6, and EDG-8 (also respectively termed S1P1, S1P3, S1P2, S1P4, and S1P5) are identified as receptors specific for sphingosine-1-phosphate (S1P). EDG2, EDG4, and EDG7 (also termed LPA1, LPA2, and LPA3, respectively) are receptors specific for lysophosphatidic (LPA). Among the S1P receptor isotypes, EDG-1, EDG-3 and EDG-5 are widely expressed in various tissues, whereas the expression of EDG-6 is confined largely to lymphoid tissues and platelets, and that of EDG-8 to the central nervous system. EDG receptors are responsible for signal transduction and are thought to play an important role in cell processes involving cell development, proliferation, maintenance, migration, differentiation, plasticity and apoptosis. Certain EDG receptors are associated with diseases mediated by lymphocyte interactions, for example, in transplantation rejection, autoimmune diseases, inflammatory diseases, infectious diseases and cancer. An alteration in EDG receptor activity contributes to the pathology and/or symptomology of these diseases. Accordingly, molecules that themselves alter the activity of EDG receptors are useful as therapeutic agents in the treatment of such diseases.

SUMMARY OF THE INVENTION

This application relates to compounds of Formula I:



in which:

n is chosen from 0, 1 and 2; m is chosen from 1, 2 and 3;

R_1 is chosen from C_{6-10}aryl and C_{5-10}heteroaryl; wherein any aryl or heteroaryl of R_1 is optionally substituted by a radical chosen from C_{6-10}arylC_{0-4}alkyl, C_{5-6}heteroarylC_{0-4}alkyl, C_{3-8}cycloalkylC_{0-4}alkyl, C_{3-8}heterocycloalkylC_{0-4}alkyl or C_{1-10}alkyl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl group of R_1 can be optionally substituted by 1 to 5 radicals chosen from halo, C_{1-10}alkyl, C_{1-10}alkoxy, halo-substituted-C_{1-10}alkyl and halo-substituted-C_{1-10}alkoxy; and any alkyl group of R_1 can optionally have a methylene replaced by an atom or group chosen from –S–, –S(O)–, –$S(O)_2$–, –NR_7– and –O–; wherein R_7 is chosen from hydrogen and C_{1-6}alkyl;

R_2, R_3, R_4 and R_5 are independently chosen from hydrogen, halo, hydroxy, C_{1-10}alkyl, C_{1-10}alkoxy, halo-substituted-C_{1-10}alkyl and halo-substituted-C_{1-10}alkoxy;

A is chosen from $-X_1C(O)OR_7$, $-X_1OP(O)(OR_7)_2$, $-X_1P(O)(OR_7)_2$, $-X_1P(O)OR_7$, $-X_1S(O)_2OR_7$, $-X_1P(O)(R_7)OR_7$ and 1*H*-tetrazol-5-yl; wherein X_1 is chosen from a bond, C_{1-3}alkylene and C_{2-3}alkenylene and R_7 is chosen from hydrogen and C_{1-6}alkyl;

B is CR_8R_9; wherein R_8 and R_9 are independently chosen from hydrogen, hydroxy, C_{1-10}alkyl, C_{1-10}alkoxy, halo-substituted-C_{1-10}alkyl and halo-substituted-C_{1-10}alkoxy;

E is chosen from CR_8 or N; wherein R_8 is chosen from hydrogen, hydroxy, C_{1-10}alkyl, C_{1-10}alkoxy, halo-substituted-C_{1-10}alkyl and halo-substituted-C_{1-10}alkoxy; or B is CR_9 and E is carbon and B and E are connected via a double bond;

X is a bond or is chosen from $-X_1OX_2-$, $-X_1NR_7X_2-$, $-X_1C(O)NR_7X_2-$, $-X_1NR_7C(O)X_2-$, $-X_1S(O)X_2-$, $-X_1S(O)_2X_2-$, $-X_1SX_2-$, C_{4-6}heteroarylene and $-X_1ON=C(R_7)X_2-$; wherein X_1 and X_2 are independently chosen from a bond, C_{1-3}alkylene and C_{2-3}alkenylene; R_7 is chosen from hydrogen and C_{1-6}alkyl; and any heteroarylene of X is optionally substituted by a member of the group chosen from halo and C_{1-6}alkyl;

Y is chosen from C_{6-10}aryl and C_{5-10}heteroaryl, wherein any aryl or heteroaryl of Y can be optionally substituted with 1 to 3 radicals chosen from halo, hydoxy, nitro, C_{1-10}alkyl, C_{1-10}alkoxy, halo-substituted C_{1-10}alkyl and halo-substituted C_{1-10}alkoxy; and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates (e.g. hydrates) of such compounds.

A second aspect of the invention is a pharmaceutical composition which contains a compound of Formula I or an N-oxide derivative, individual isomer or mixture of isomers thereof, or a pharmaceutically acceptable salt thereof, in admixture with one or more suitable excipients.

A third aspect of the invention is a method for treating a disease in an animal in which alteration of EDG receptor mediated signal transduction can prevent, inhibit or ameliorate the pathology and/or symptomology of the disease, which method comprises administering to the animal a therapeutically effective amount of a compound of Formula I or a N-oxide derivative, individual isomer or mixture of isomers thereof; or a pharmaceutically acceptable salt thereof.

A fourth aspect of the invention is the use of a compound of Formula I in the manufacture of a medicament for treating a disease in an animal in which alteration of EDG receptor mediated signal transduction contributes to the pathology and/or symptomology of the disease.

A fifth aspect of the invention is a process for preparing compounds of Formula I and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts thereof.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The invention provides compounds that are useful in the treatment and/or prevention of diseases or disorders mediated by lymphocyte interactions. Also provided are methods for treating such diseases or disorders.

Definitions

In this specification, unless otherwise defined:

"Alkyl" as a group and as a structural element of other groups, for example halo-substituted-alkyl, alkoxy, acyl, alkylthio, alkylsulfonyl and alkylsulfinyl, can be either straight-chained or branched. "Alkenyl" as a group and as a structural element of other groups contains one or more carbon-carbon double bonds, and can be either straight-chain, or branched. Any double bonds can be in the cis- or trans- configuration. A preferred alkenyl group is vinyl. "Alkynyl" as a group and as structural element of other groups and compounds contains at least one C ≡C triple bond and can also contain one or more C=C double bonds, and can, so far as possible, be either straight-chain or branched. A preferred alkynyl group is propargyl. Any cycloalkyl group, alone or as a structural element of other groups can contain from 3 to 8 carbon atoms, preferably from 3 to 6 carbon atoms. "Alkylene" and "alkenylene" are divalent radicals derived from "alkyl" and "alkenyl" groups, respectively. In this application, any alkyl group of R^1 can be optionally interrupted by a member of the group selected from –S–, –S(O)–, –$S(O)_2$–, –NR^3– and –O– (wherein R^3 is hydrogen or C_{1-6}alkyl). These groups include –CH_2–O–CH_2–, –CH_2–$S(O)_2$–CH_2–, –$(CH_2)_2$–NR^3–CH_2–, –CH_2–O–$(CH_2)_2$–, and the like.

"Aryl" means a monocyclic or fused bicyclic aromatic ring assembly containing six to ten ring carbon atoms. For example, C_{6-12}aryl can be phenyl, biphenyl or naphthyl, preferably phenyl. "Arylene" means a divalent radical derived from an aryl group. For example, arylene as used in this application can be phenylene, biphenylene, naphthylene and the like.

"Halo" or "halogen" means F, Cl, Br or I, preferably F or Cl. Halo-substituted alkyl groups and compounds can be partially halogenated or perhalogenated, whereby in the case of multiple halogenation, the halogen substituents can be identical or different. A preferred perhalogenated alkyl group is for example trifluoromethyl.

"Heteroaryl" means aryl, as defined in this application, provided that one or more of the ring carbon atoms indicated are replaced by a hetero atom moiety selected from N, O or S, and each ring is comprised of 5 to 6 ring atoms, unless otherwise stated. For example, heteroaryl as used in this application includes thiophenyl, pyridinyl, furanyl, isoxazolyl, benzoxazolyl or benzo[1,3]dioxolyl, preferably thiophenyl, furanyl or pyridinyl. "Heteroarylene" means heteroaryl, as defined in this application, provided that the ring assembly comprises a divalent radical.

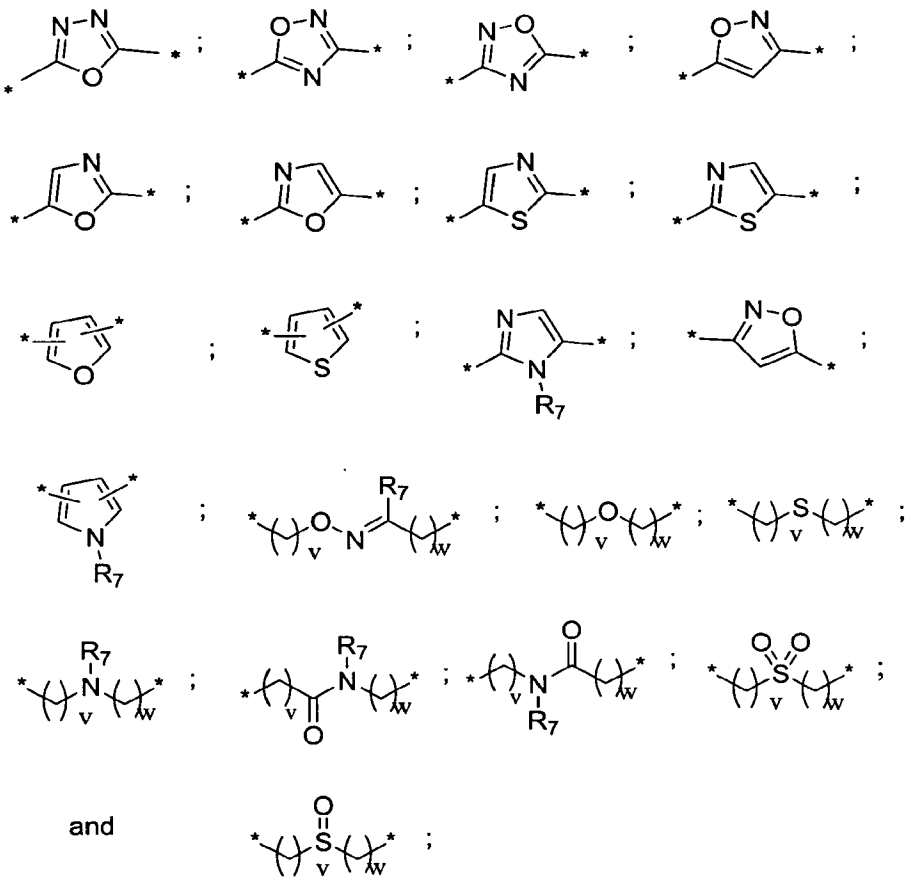
As used in the present invention, an EDG-1 selective compound (agent or modulator) has a specificity that is selective for EDG-1 over EDG-3 and over one or more of EDG-5, EDG-6, and EDG-8. As used herein, selectivity for one EDG receptor (a "selective receptor") over another EDG receptor (a "non-selective receptor") means that the compound has a much higher potency in inducing activities mediated by the selective EDG receptor (e.g., EDG-1) than that for the non-selective S1P-specific EDG receptor. If measured in a GTP-γS binding assay (as described in the Example below), an EDG-1 selective compound typically has an EC50 (effective concentration that causes 50% of the maximum response) for a selective receptor (EDG-1) that is at least 5, 10, 25, 50, 100, 500, or 1000 fold lower than its EC50 for a non-selective receptor (e.g., one or more of EDG-3, EDG-5, EDG-6, and EDG-8).

Detailed Description of the Invention

The invention provides compounds that are useful for treating or preventing diseases or disorders that are mediated by lymphocyte interactions. In one embodiment, for compounds of Formula I, R_1 is chosen from phenyl, naphthyl and thiophenyl optionally substituted by C_{6-10}arylC_{0-4}alkyl, C_{5-6}heteroarylC_{0-4}alkyl, C_{3-8}cycloalkylC_{0-4}alkyl, C_{3-8}heterocycloalkylC_{0-4}alkyl or C_{1-10}alkyl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl group of R_1 can be optionally substituted by 1 to 5 radicals chosen from halo, C_{1-10}alkyl, C_{1-10}alkoxy, halo-substituted-C_{1-10}alkyl and halo-substituted-C_{1-10}alkoxy; and any alkyl group of R_1 can optionally have a methylene replaced by an atom or group chosen from –S–, –S(O)–, –S(O)$_2$–, –NR$_7$– and –O–; wherein R_7 is hydrogen or C_{1-6}alkyl.

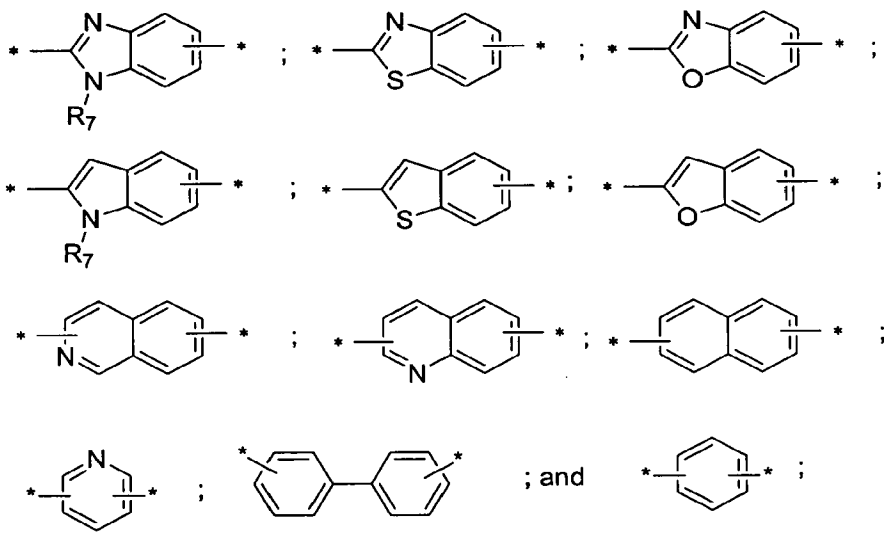
In another embodiment, A is chosen from $-X_1C(O)OR_7$ and 1*H*-tetrazol-5-yl; wherein X_1 is chosen from a bond, C_{1-3}alkylene and C_{2-3}alkenylene and R_7 is chosen from hydrogen and C_{1-6}alkyl.

In a further embodiment, X is chosen from:



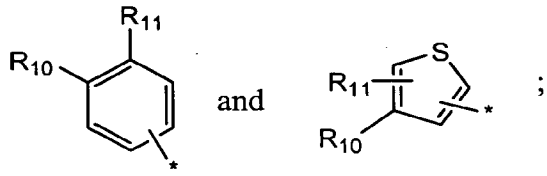
wherein the left and right asterisks of X indicate the point of attachment between R_1 and Y of Formula I, respectively; R_7 is chosen from hydrogen and C_{1-6}alkyl; v and w are independently 0, 1, 2 or 3.

In another embodiment, Y is chosen from:



wherein R_7 is hydrogen or C_{1-6}alkyl; and the left and right asterisks of Y indicate the point of attachment between X and E of Formula I, respectively.

In a further embodiment, R_1 is chosen from:



wherein the asterisk is the point of attachment of R_1 with X; R_{10} is C_{6-10}arylC_{0-4}alkyl, C_{5-6}heteroarylC_{0-4}alkyl, C_{3-8}cycloalkylC_{0-4}alkyl, C_{3-8}heterocycloalkylC_{0-4}alkyl or C_{1-10}alkyl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl group of R_{10} can be optionally substituted by 1 to 3 radicals chosen from halo, C_{1-10}alkyl, C_{1-10}alkoxy, halo-substituted-C_{1-10}alkyl and halo-substituted-C_{1-10}alkoxy; and any alkyl group of R_{10} can optionally have a methylene replaced by an atom or group chosen from –S–, –S(O)–, –$S(O)_2$–, –NR_7– and –O–; wherein R_7 is hydrogen or C_{1-6}alkyl; and R_{11} is selected from halo, C_{1-10}alkyl, C_{1-10}alkoxy, halo-substituted-C_{1-10}alkyl and halo-substituted-C_{1-10}alkoxy.

Preferred compounds are shown in the examples and table 1, infra.

The invention provides forms of the compound that have the hydroxyl or amine group present in a protected form; these function as prodrugs. Prodrugs are compounds that are converted into an active drug form after administration, through one or more chemical or biochemical transformations. Forms of the compounds of the present invention that are

readily converted into the claimed compound under physiological conditions are prodrugs of the claimed compounds and are within the scope of the present invention. Examples of prodrugs include forms where a hydroxyl group is acylated to form a relatively labile ester such as an acetate ester, and forms where an amine group is acylated with the carboxylate group of glycine or an L-amino acid such as serine, forming an amide bond that is particularly susceptible to hydrolysis by common metabolic enzymes.

Compounds of Formula I can exist in free form or in salt form, e.g. addition salts with inorganic or organic acids. Where hydroxyl groups are present, these groups can also be present in salt form, e.g. an ammonium salt or salts with metals such as lithium, sodium, potassium, calcium, zinc or magnesium, or a mixture thereof. Compounds of Formula I and their salts in hydrate or solvate form are also part of the invention.

When the compounds of Formula I have asymmetric centers in the molecule, various optical isomers are obtained. The present invention also encompasses enantiomers, racemates, diastereoisomers and mixtures thereof. Moreover, when the compounds of Formula I include geometric isomers, the present invention embraces cis-compounds, trans-compounds and mixtures thereof. Similar considerations apply in relation to starting materials exhibiting asymmetric carbon atoms or unsaturated bonds as mentioned above.

Methods and Pharmaceutical Compositions for Treating Immunomodulatory Conditions

The compounds of Formula I in free form or in pharmaceutically acceptable salt form, exhibit valuable pharmacological properties, e.g. lymphocyte recirculation modulating properties, for example, as indicated by the *in vitro* and *in vivo* tests of Example 56 and are therefore indicated for therapy. Compounds of Formula I preferably show an EC_{50} in the range of 1×10^{-11} to 1×10^{-5} M, preferably less than 50nM. The compounds exhibit selectivity for one or more EDG/S1P receptors, preferably EDG-1/S1P-1. EDG-1/S1P-1 selective modulators of the present invention can be identified by assaying a compound's binding to EDG-1/S1P-1 and one or more of the other EDG/S1P receptors (e.g., EDG-3/S1P-3, EDG-5/S1P-2, EDG-6/S1P-4, and EDG-8/S1P-5). An EDG-1/S1P-1 selective modulator usually has an EC50 for the EDG-1/S1P-1 receptor in the range of 1×10^{-11} to 1×10^{-5} M, preferably less than 50 nM, more preferably less than 5 nM. It also has an EC50 for one or more of the other EDG/S1P receptors that is at least 5, 10, 25, 50, 100,

500, or 1000 fold higher than its EC50 for EDG-1/S1P-1. Thus, some of the EDG-1/S1P-1 modulatory compounds will have an EC50 for EDG-1/S1P-1 that is less than 5 nM while their EC50 for one or more of the other EDG/S1P receptors are at least 100 nM or higher. Other than assaying binding activity to the EDG/S1P receptors, EDG-1/S1P-1 selective agents can also be identified by examining a test agent's ability to modify a cellular process or activity mediated by an EDG/S1P receptor.

The compounds of formula I are, therefore, useful in the treatment and/or prevention of diseases or disorders mediated by lymphocytes interactions, for example in transplantation, such as acute or chronic rejection of cell, tissue or organ allo- or xenografts or delayed graft function, graft versus host disease, autoimmune diseases, e.g. rheumatoid arthritis, systemic lupus erythematosus, hashimoto's thyroidis, multiple sclerosis, myasthenia gravis, diabetes type I or II and the disorders associated therewith, vasculitis, pernicious anemia, Sjoegren syndrome, uveitis, psoriasis, Graves ophthalmopathy, alopecia areata and others, allergic diseases, e.g. allergic asthma, atopic dermatitis, allergic rhinitis/conjunctivitis, allergic contact dermatitis, inflammatory diseases optionally with underlying aberrant reactions, e.g. inflammatory bowel disease, Crohn's disease or ulcerative colitis, intrinsic asthma, inflammatory lung injury, inflammatory liver injury, inflammatory glomerular injury, atherosclerosis, osteoarthritis, irritant contact dermatitis and further eczematous dermatitises, seborrhoeic dermatitis, cutaneous manifestations of immunologically-mediated disorders, inflammatory eye disease, keratoconjunctivitis, myocarditis or hepatitis, ischemia/reperfusion injury, e.g. myocardial infarction, stroke, gut ischemia, renal failure or hemorrhage shock, traumatic shock, T cell lymphomas or T cell leukemias, infectious diseases, e.g. toxic shock (e.g. superantigen induced), septic shock, adult respiratory distress syndrome or viral infections, e.g. AIDS, viral hepatitis, chronic bacterial infection, or senile dementia. Examples of cell, tissue or solid organ transplants include e.g. pancreatic islets, stem cells, bone marrow, corneal tissue, neuronal tissue, heart, lung, combined heart-lung, kidney, liver, bowel, pancreas, trachea or oesophagus. For the above uses the required dosage will of course vary depending on the mode of administration, the particular condition to be treated and the effect desired.

Furthermore, the compounds of formula I are useful in cancer chemotherapy, particularly for cancer chemotherapy of solid tumors, e.g. breast cancer, or as an anti-angiogenic agent.

The required dosage will of course vary depending on the mode of administration, the particular condition to be treated and the effect desired. In general, satisfactory results are indicated to be obtained systemically at daily dosages of from about 0.03 to 2.5 mg/kg per body weight. An indicated daily dosage in the larger mammal, e.g. humans, is in the range from about 0.5 mg to about 100 mg, conveniently administered, for example, in divided doses up to four times a day or in retard form. Suitable unit dosage forms for oral administration comprise from ca. 1 to 50 mg active ingredient.

The compounds of Formula I can be administered by any conventional route, in particular enterally, for example, orally, e.g. in the form of tablets or capsules, or parenterally, for example, in the form of injectable solutions or suspensions, topically, e.g. in the form of lotions, gels, ointments or creams, or in a nasal or a suppository form. Pharmaceutical compositions comprising a compound of Formula I in free form or in pharmaceutically acceptable salt form in association with at least one pharmaceutical acceptable carrier or diluent can be manufactured in conventional manner by mixing with a pharmaceutically acceptable carrier or diluent.

The compounds of Formula I can be administered in free form or in pharmaceutically acceptable salt form, for example, as indicated above. Such salts can be prepared in a conventional manner and exhibit the same order of activity as the free compounds.

In accordance with the foregoing the present invention further provides:

1.1 A method for preventing or treating disorders or diseases mediated by lymphocytes, e.g. such as indicated above, in a subject in need of such treatment, which method comprises administering to said subject an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof;

1.2 A method for preventing or treating acute or chronic transplant rejection or T-cell mediated inflammatory or autoimmune diseases, e.g. as indicated above, in a subject in need of such treatment, which method comprises administering to said subject an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof;

1.3 A method for inhibiting or controlling deregulated angiogenesis, e.g. sphingosine-1-phosphate (S1P) mediated angiogenesis, in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

1.4 A method for preventing or treating diseases mediated by a neo-angiogenesis process or associated with deregulated angiogenesis in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

2. A compound of formula I, in free form or in a pharmaceutically acceptable salt form for use as a pharmaceutical, e.g. in any of the methods as indicated under 1.1 to 1.4 above.

3. A pharmaceutical composition, e.g. for use in any of the methods as in 1.1 to 1.4 above comprising a compound of formula I in free form or pharmaceutically acceptable salt form in association with a pharmaceutically acceptable diluent or carrier therefor.

4. A compound of formula I or a pharmaceutically acceptable salt thereof for use in the preparation of a pharmaceutical composition for use in any of the method as in 1.1 to 1.4 above.

The compounds of formula I may be administered as the sole active ingredient or in conjunction with, e.g. as an adjuvant to, other drugs e.g. immunosuppressive or immunomodulating agents or other anti-inflammatory agents, e.g. for the treatment or prevention of allo- or xenograft acute or chronic rejection or inflammatory or autoimmune disorders, or a chemotherapeutic agent, e.g. a malignant cell anti-proliferative agent. For example the compounds of formula I may be used in combination with a calcineurin inhibitor, e.g. cyclosporin A or FK 506; a mTOR inhibitor, e.g. rapamycin, 40-O-(2-hydroxyethyl)-rapamycin, CCI779, ABT578 or AP23573; an ascomycin having immunosuppressive properties, e.g. ABT-281, ASM981, etc.; corticosteroids; cyclophosphamide; azathioprene; methotrexate; leflunomide; mizoribine; mycophenolic acid; mycophenolate mofetil; 15-deoxyspergualine or an immunosuppressive homologue, analogue or derivative thereof; immunosuppressive monoclonal antibodies, e.g. monoclonal antibodies to leukocyte receptors, e.g. MHC, CD2, CD3, CD4, CD7, CD8, CD25, CD28, CD40. CD45, CD58, CD80, CD86 or their ligands; other immunomodulatory compounds,

e.g. a recombinant binding molecule having at least a portion of the extracellular domain of CTLA4 or a mutant thereof, e.g. an at least extracellular portion of CTLA4 or a mutant thereof joined to a non-CTLA4 protein sequence, e.g. CTLA4Ig (for ex. designated ATCC 68629) or a mutant thereof, e.g. LEA29Y ; adhesion molecule inhibitors, e.g. LFA-1 antagonists, ICAM-1 or -3 antagonists, VCAM-4 antagonists or VLA-4 antagonists; or a chemotherapeutic agent.

By the term "chemotherapeutic agent" is meant any chemotherapeutic agent and it includes but is not limited to,

i. an aromatase inhibitor,

ii. an anti-estrogen, an anti-androgen (especially in the case of prostate cancer) or a gonadorelin agonist,

iii. a topoisomerase I inhibitor or a topoisomerase II inhibitor,

iv. a microtubule active agent, an alkylating agent, an antineoplastic antimetabolite or a platin compound,

v. a compound targeting/decreasing a protein or lipid kinase activity or a protein or lipid phosphatase activity, a further anti-angiogenic compound or a compound which induces cell differentiation processes,

vi. a bradykinin 1 receptor or an angiotensin II antagonist,

vii. a cyclooxygenase inhibitor, a bisphosphonate, a histone deacetylase inhibitor, a heparanase inhibitor (prevents heparan sulphate degradation), e.g. PI-88, a biological response modifier, preferably a lymphokine or interferons, e.g. interferon □, an ubiquitination inhibitor, or an inhibitor which blocks anti-apoptotic pathways,

viii. an inhibitor of Ras oncogenic isoforms, e.g. H-Ras, K-Ras or N-Ras, or a farnesyl transferase inhibitor, e.g. L-744,832 or DK8G557,

ix. a telomerase inhibitor, e.g. telomestatin,

x. a protease inhibitor, a matrix metalloproteinase inhibitor, a methionine aminopeptidase inhibitor, e.g. bengamide or a derivative thereof, or a proteosome inhibitor, e.g. PS-341, and/or

xi. a mTOR inhibitor.

The term "aromatase inhibitor" as used herein relates to a compound which inhibits the estrogen production, i.e. the conversion of the substrates androstenedione and testo-

sterone to estrone and estradiol, respectively. The term includes, but is not limited to steroids, especially atamestane, exemestane and formestane and, in particular, non-steroids, especially aminoglutethimide, roglethimide, pyridoglutethimide, trilostane, testolactone, ketokonazole, vorozole, fadrozole, anastrozole and letrozole. A combination of the invention comprising a chemotherapeutic agent which is an aromatase inhibitor is particularly useful for the treatment of hormone receptor positive tumors, e.g. breast tumors.

The term "anti-estrogen" as used herein relates to a compound which antagonizes the effect of estrogens at the estrogen receptor level. The term includes, but is not limited to tamoxifen, fulvestrant, raloxifene and raloxifene hydrochloride. A combination of the invention comprising a chemotherapeutic agent which is an anti-estrogen is particularly useful for the treatment of estrogen receptor positive tumors, e.g. breast tumors.

The term "anti-androgen" as used herein relates to any substance which is capable of inhibiting the biological effects of androgenic hormones and includes, but is not limited to, bicalutamide.

The term "gonadorelin agonist" as used herein includes, but is not limited to abarelix, goserelin and goserelin acetate.

The term "topoisomerase I inhibitor" as used herein includes, but is not limited to topotecan, irinotecan, 9-nitrocamptothecin and the macromolecular camptothecin conjugate PNU-166148 (compound A1 in WO99/17804).

The term "topoisomerase II inhibitor" as used herein includes, but is not limited to the anthracyclines such as doxorubicin, daunorubicin, epirubicin, idarubicin and nemorubicin, the anthraquinones mitoxantrone and losoxantrone, and the podophillotoxines etoposide and teniposide.

The term "microtubule active agent" relates to microtubule stabilizing and microtubule destabilizing agents including, but not limited to taxanes, e.g. paclitaxel and docetaxel, vinca alkaloids, e.g., vinblastine, especially vinblastine sulfate, vincristine especially vincristine sulfate, and vinorelbine, discodermolides and epothilones and derivatives thereof, e.g. epothilone B or a derivative thereof.

The term "alkylating agent" as used herein includes, but is not limited to busulfan, chlorambucil, cyclophosphamide, ifosfamide, melphalan or nitrosourea (BCNU or Gliadel™).

The term "antineoplastic antimetabolite" includes, but is not limited to 5-fluorouracil, capecitabine, gemcitabine, cytarabine, fludarabine, thioguanine, methotrexate and edatrexate.

The term "platin compound" as used herein includes, but is not limited to carboplatin, cis-platin and oxaliplatin.

The term "compounds targeting/decreasing a protein or lipid kinase activity or further anti-angiogenic compounds" as used herein includes, but is not limited to protein tyrosine kinase and/or serine and/or threonine kinase inhibitors or lipid kinase inhibitors, e.g. compounds targeting, decreasing or inhibiting the activity of the epidermal growth factor family of receptor tyrosine kinases (EGFR, ErbB2, ErbB3, ErbB4 as homo- or heterodimers), the vascular endothelial growth factor family of receptor tyrosine kinases (VEGFR), the platelet-derived growth factor-receptors (PDGFR), the fibroblast growth factor-receptors (FGFR), the insulin-like growth factor receptor 1 (IGF-1R), the Trk receptor tyrosine kinase family, the Axl receptor tyrosine kinase family, the Ret receptor tyrosine kinase, the Kit/SCFR receptor tyrosine kinase, members of the c-Abl family and their gene-fusion products (e.g. BCR-Abl), members of the protein kinase C (PKC) and Raf family of serine/threonine kinases, members of the MEK, SRC, JAK, FAK, PDK or PI(3) kinase family, or of the PI(3)-kinase-related kinase family, and/or members of the cyclin-dependent kinase family (CDK) and anti-angiogenic compounds having another mechanism for their activity, e.g. unrelated to protein or lipid kinase inhibition.

Compounds which target, decrease or inhibit the activity of VEGFR are especially compounds, proteins or antibodies which inhibit the VEGF receptor tyrosine kinase, inhibit a VEGF receptor or bind to VEGF, and are in particular those compounds, proteins or monoclonal antibodies generically and specifically disclosed in WO 98/35958, e.g. 1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine or a pharmaceutically acceptable salt thereof, e.g. the succinate, in WO 00/27820, e.g. a N-aryl(thio) anthranilic acid amide derivative e.g. 2-[(4-pyridyl)methyl]amino-N-[3-methoxy-5-(trifluoromethyl)phenyl]benzamide or 2-[(1-oxido-4-pyridyl)methyl]amino-N-[3-trifluoromethylphenyl]benzamide, or in WO 00/09495, WO 00/59509, WO 98/11223, WO 00/27819 and EP 0 769 947; those as described by M. Prewett et al in Cancer Research 59 (1999) 5209-5218, by F. Yuan et al in Proc. Natl. Acad. Sci. USA, vol. 93, pp. 14765-14770, Dec. 1996, by Z. Zhu et al in Cancer Res. 58, 1998,

3209-3214, and by J. Mordenti et al in Toxicologic Pathology, Vol. 27; no. 1, pp 14-21, 1999; in WO 00/37502 and WO 94/10202; Angiostatin™, described by M. S. O'Reilly et al, Cell 79, 1994, 315-328; Endostatin™, described by M. S. O'Reilly et al, Cell 88, 1997, 277-285; anthranilic acid amides; ZD4190; ZD6474; SU5416; SU6668; or anti-VEGF antibodies or anti-VEGF receptor antibodies,e.g. RhuMab.

By antibody is meant intact monoclonal antibodies, polyclonal antibodies, multispecific antibodies formed from at least 2 intact antibodies, and antibody fragments so long as they exhibit the desired biological activity.

Compounds which target, decrease or inhibit the activity of the epidermal growth factor receptor family are especially compounds, proteins or antibodies which inhibit members of the EGF receptor tyrosine kinase family, e.g. EGF receptor, ErbB2, ErbB3 and ErbB4 or bind to EGF or EGF related ligands, or which have a dual inhibiting effect on the ErbB and VEGF receptor kinase and are in particular those compounds, proteins or monoclonal antibodies generically and specifically disclosed in WO 97/02266, e.g. the compound of ex. 39, or in EP 0 564 409, WO 99/03854, EP 0520722, EP 0 566 226, EP 0 787 722, EP 0 837 063, US 5,747,498, WO 98/10767, WO 97/30034, WO 97/49688, WO 97/38983 and, especially, WO 96/30347 (e.g. compound known as CP 358774), WO 96/33980 (e.g. compound ZD 1839) and WO 95/03283 (e.g. compound ZM105180) or PCT/EP02/08780; e.g. trastuzumab (Herpetin^{R}), cetuximab, Iressa, OSI-774, CI-1033, EKB-569, GW-2016, E1.1, E2.4, E2.5, E6.2, E6.4, E2.11, E6.3 or E7.6.3.

Compounds which target, decrease or inhibit the activity of PDGFR are especially compounds which inhibit the PDGF receptor, e.g. a N-phenyl-2-pyrimidine-amine derivative, e.g. imatinib.

Compounds which target, decrease or inhibit the activity of c-AbI family members and their gene fusion products are, e.g. a N-phenyl-2-pyrimidine-amine derivative, e.g. imatinib; PD180970; AG957; or NSC 680410.

Compounds which target, decrease or inhibit the activity of protein kinase C, Raf, MEK, SRC, JAK, FAK and PDK family members, or PI(3) kinase or PI(3) kinase-related family members, and/or members of the cyclin-dependent kinase family (CDK) are especially those staurosporine derivatives disclosed in EP 0 296 110, e.g. midostaurin; examples of further compounds include e.g. UCN-01, safingol, BAY 43-9006, Bryostatin 1,

Perifosine; Ilmofosine; RO 318220 and RO 320432; GO 6976; Isis 3521; or LY333531/LY379196.

Further anti-angiogenic compounds are e.g. thalidomide (THALOMID) and TNP-470.

Compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase are, e.g. inhibitors of phosphatase 1, phosphatase 2A, PTEN or CDC25, e.g. okadaic acid or a derivative thereof.

Compounds which induce cell differentiation processes are, e.g. retinoic acid, α-, γ- or δ-tocopherol or α-, γ- or δ-tocotrienol.

The term cyclooxygenase inhibitor as used herein includes, but is not limited to, e.g. celecoxib (Celebrex^R), rofecoxib (Vioxx^R), etoricoxib, valdecoxib or a 5-alkyl-2-arylaminophenylacetic acid, e.g. 5-methyl-2-(2'-chloro-6'-fluoroanilino)phenyl acetic acid.

The term "histone deacetylase inhibitor" as used herein includes, but is not limited to MS-27-275, SAHA, pyroxamide, FR-901228 or valproic acid.

The term "bisphosphonates" as used herein includes, but is not limited to, etridonic, clodronic, tiludronic, pamidronic, alendronic, ibandronic, risedronic and zoledronic acid.

The term "matrix metalloproteinase inhibitor" as used herein includes, but is not limited to collagen peptidomimetic and non-petidomimetic inhibitors, tetracycline derivatives, e.g. hydroxamate peptidomimetic inhibitor batimastat and its orally bioavailable analogue marimastat, prinomastat, BMS-279251, BAY 12-9566, TAA211 or AAJ996.

The term "mTOR inhibitor" as used herein includes, but is not limited to rapamycin (sirolimus) or a derivative thereof, e.g. 32-deoxorapamycin, 16-pent-2-ynyloxy-32-deoxorapamycin, 16-pent-2-ynyloxy-32(S)-dihydro-rapamycin, 16-pent-2-ynyloxy-32(S)-dihydro-40-O-(2-hydroxyethyl)-rapamycin and, more preferably, 40-0-(2-hydroxy-ethyl)-rapamycin. Further examples of rapamycin derivatives include e.g. CCI779 or 40- [3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate]-rapamycin or a pharmaceutically acceptable salt thereof, as disclosed in USP 5,362,718, ABT578 or 40-(tetrazolyl)-rapamycin, particularly 40-epi-(tetrazolyl)-rapamycin, e.g. as disclosed in WO 99/15530, or rapalogs as disclosed e.g. in WO 98/02441 and WO01/14387, e.g. AP23573.

Where the compounds of formula I are administered in conjunction with other immunosuppressive / immunomodulatory, anti-inflammatory or chemotherapeutic therapy,

dosages of the co-administered immunosuppressant, immunomodulatory, anti-inflammatory or chemotherapeutic compound will of course vary depending on the type of co-drug employed, e.g. whether it is a steroid or a calcineurin inhibitor, on the specific drug employed, on the condition being treated and so forth.

In accordance with the foregoing the present invention provides in a yet further aspect:

5. A method as defined above comprising co-administration, e.g. concomitantly or in sequence, of a therapeutically effective non-toxic amount of a compound of formula I and at least a second drug substance, e.g. an immunosuppressant, immunomodulatory, anti-inflammatory or chemotherapeutic drug, e.g. as indicated above.

6. A pharmaceutical combination, e.g. a kit, comprising a) a first agent which is a compound of formula I as disclosed herein, in free form or in pharmaceutically acceptable salt form, and b) at least one co-agent, e.g. an immunosuppressant, immunomodulatory, anti-inflammatory or chemotherapeutic drug, e.g. as disclosed above. The kit may comprise instructions for its administration.

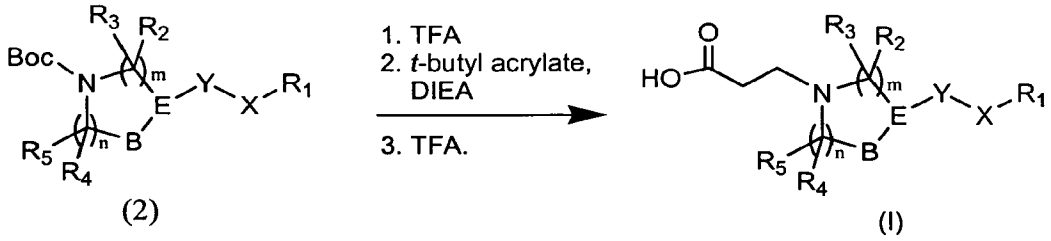
The terms "co-administration" or "combined administration" or the like as utilized herein are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time.

The term "pharmaceutical combination" as used herein means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that the active ingredients, e.g. a compound of formula I and a co-agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that the active ingredients, e.g. a compound of formula I and a co-agent, are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the 2 compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of 3 or more active ingredients.

Methods for Preparing Compounds of the Invention

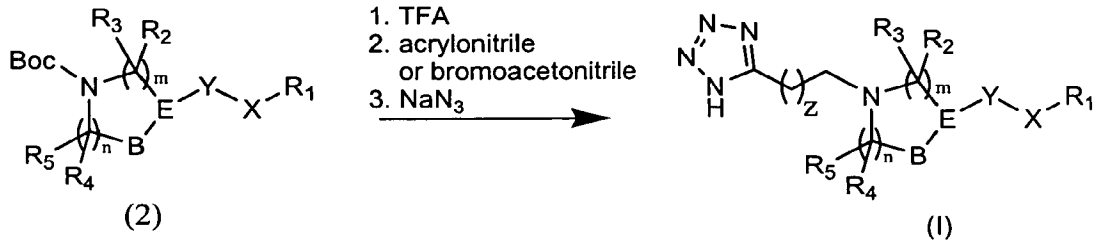
The present invention also includes processes for the preparation of immunomodulatory compounds of the invention. In the reactions described, it can be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups can be used in accordance with standard practice, for example, see T.W. Greene and P. G. M. Wuts in "Protective Groups in Organic Chemistry", John Wiley and Sons, 1991.

Compounds of Formula I, in which A is 2-carboxy-ethyl, can be prepared by proceeding as in the following reaction scheme:



in which B, E, X, Y, R_1 R_2, R_3, R_4 and R_5 are as defined for Formula I above. Compounds of Formula I can be prepared sequentially by treating a compound of formula 2 with a suitable acid (e.g. TFA, and the like), reacting with *t*-butyl acrylate in the presence of a suitable amine (e.g. DIEA, and the like) and removing the *t*-butyl protecting group with a suitable acid (e.g. TFA, and the like). The reaction proceeds at a temperature of about 0 to about 120°C and can take up to about 24 hours to complete.

Compounds of Formula I, in which A is 1*H*-tetrazol-5-ylalkyl, can be prepared by proceeding as in the following reaction scheme:



in which B, E, X, Y, R_1 R_2, R_3, R_4 and R_5 are as defined for Formula I above, Z is 0 or 1. Compounds of Formula I can be prepared sequentially by treating a compound of formula 2 with a suitable acid (e.g. TFA, and the like), reacting with acrylonitrile or bromoacetonitrile in the presence of a suitable base (e.g. NaOAc, and the like) and followed by reacting with NaN_3 in a suitable solvent (e.g. DMF, and the like). The reactions proceed at a temperature of about 0 to about 120°C and can take up to about 24 hours to complete.

Additional Processes for Preparing Compounds of the Invention:

A compound of the invention can be prepared as a pharmaceutically acceptable acid addition salt by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid. Alternatively, a pharmaceutically acceptable base addition salt of a compound of the invention can be prepared by reacting the free acid form of the compound with a pharmaceutically acceptable inorganic or organic base. Alternatively, the salt forms of the compounds of the invention can be prepared using salts of the starting materials or intermediates.

The free acid or free base forms of the compounds of the invention can be prepared from the corresponding base addition salt or acid addition salt from, respectively. For example a compound of the invention in an acid addition salt form can be converted to the corresponding free base by treating with a suitable base (e.g., ammonium hydroxide solution, sodium hydroxide, and the like). A compound of the invention in a base addition salt form can be converted to the corresponding free acid by treating with a suitable acid (e.g., hydrochloric acid, etc.).

Compounds of the invention in unoxidized form can be prepared from N-oxides of compounds of the invention by treating with a reducing agent (e.g., sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, phosphorus trichloride, tribromide, or the like) in a suitable inert organic solvent (e.g. acetonitrile, ethanol, aqueous dioxane, or the like) at 0 to 80°C.

Prodrug derivatives of the compounds of the invention can be prepared by methods known to those of ordinary skill in the art (e.g., for further details see Saulnier et al., (1994), Bioorganic and Medicinal Chemistry Letters, Vol. 4, p. 1985). For example, appropriate

prodrugs can be prepared by reacting a non-derivatized compound of the invention with a suitable carbamylating agent (e.g., 1,1-acyloxyalkylcarbanochloridate, para-nitrophenyl carbonate, or the like).

Protected derivatives of the compounds of the invention can be made by means known to those of ordinary skill in the art. A detailed description of techniques applicable to the creation of protecting groups and their removal can be found in T W. Greene, "Protecting Groups in Organic Chemistry", 3rd edition, John Wiley and Sons, Inc., 1999.

Compounds of the present invention can be conveniently prepared, or formed during the process of the invention, as solvates (e.g., hydrates). Hydrates of compounds of the present invention can be conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents such as dioxin, tetrahydrofuran or methanol.

Compounds of the invention can be prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to forma pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomers. While resolution of enantiomers can be carried out using covalent diastereomeric derivatives of the compounds of the invention, dissociable complexes are preferred (e.g., crystalline diastereomeric salts). Diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and can be readily separated by taking advantage of these dissimilarities. The diastereomers can be separated by chromatography, or preferable, by separation/resolution techniques based upon differences in solubility. The optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization. A more detailed description of the techniques applicable to the resolution of stereoisomers of compounds from the their racemic mixture can be found in Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions", John Wiley And Sons, Inc., 1981.

In summary, the compounds of Formula I can be made by a process, which involves:

(a) reacting a compound of formula 2 with either *t*-butyl acrylate, acylonitrile/NaN_3 or bromoacetonitrile/NaN_3; and

(b) optionally converting a compound of the invention into a pharmaceutically acceptable salt;

(c) optionally converting a salt form of a compound of the invention to a non-salt form;

(d) optionally converting an unoxidized form of a compound of the invention into a pharmaceutically acceptable N-oxide;

(e) optionally converting an N-oxide form of a compound of the invention to its unoxidized form;

(f) optionally resolving an individual isomer of a compound of the invention from a mixture of isomers;

(g) optionally converting a non-derivatized compound of the invention into a pharmaceutically acceptable prodrug derivative; and

(h) optionally converting a prodrug derivative of a compound of the invention to its non-derivatized form.

Insofar as the production of the starting materials is not particularly described, the compounds are known or can be prepared analogously to methods known in the art or as disclosed in the Examples hereinafter.

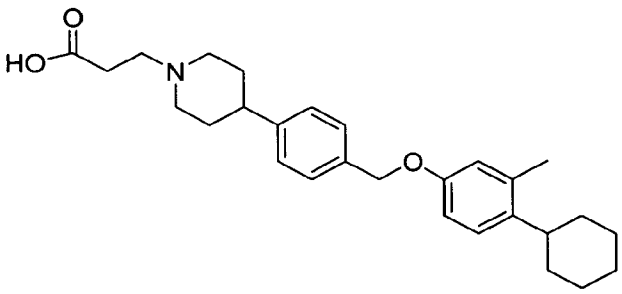
One of skill in the art will appreciate that the above transformations are only representative of methods for preparation of the compounds of the present invention, and that other well known methods can similarly be used.

EXAMPLES

The following examples provide detailed descriptions of the preparation of representative compounds and are offered to illustrate, but not to limit the present invention.

Example 1

3-{4-[4-(4-Cyclohexyl-3-methyl-phenoxymethyl)-phenyl]-piperidin-1-yl}-propionic acid



To a solution of 4-bromo-3-methyl-phenol (500 mg, 2.67 mmol, 1 eq.) in acetonitrile (5 mL) is added K_2CO_3 (1.47 g, 10.6 mmol, 4 eq.). The mixture is stirred for 30 minutes at room temperature. Iodomethane (493 mg, 1.3 eq) is then added dropwise via syringe and the mixture is stirred for 12 hours. The reaction mixture is diluted with water and extracted with ethyl acetate. The combined organic layers are washed with brine and dried over Na_2SO_4. After concentration, the residue is purified by silica gel column chromatography (5% EtOAc in hexanes) to give 1-Bromo-4-methoxy-2-methyl-benzene.

1-Bromo-4-methoxy-2-methyl-benzene (520 mg, 2.6 mmol) is dissolved in cyclohexylzinc bromide THF solution (0.5 M, 15 mL) in a microwave tube. Pd(*t*-$Bu_3P)_2$ (66 mg, 0.13 mmol, 0.05 eq.) is added to this solution. The mixture is purged with N_2 (g) for 5 minutes and heated at 100°C for 30 minutes using microwave irradiation. Upon completion, the reaction mixture is diluted with EtOAc, washed with 1N HCl (aq), brine, filtered through celite, and dried over Na_2SO_4. After concentration, the residue is partially purified by silica gel chromatography (5% EtOAc in hexanes) to give crude 1-cyclohexyl-4-methoxy-2-methyl-benzene.

To a solution of crude 1-cyclohexyl-4-methoxy-2-methyl-benzene in dry DCM (10 mL) is added BBr_3 at -78°C. Following this addition, the mixture is heated at 50°C for 12 hours. The reaction mixture is cooled in an ice bath, and the reaction is quenched by the dropwise addition of water. The mixture is extracted with DCM. The combined organic phases are washed with 10 % $NaHCO_3$ (aq), brine, and dried over Na_2SO_4. After concentration, the residue is purified by silica gel chromatography (10% EtOAc in hexanes) to give 4-cyclohexyl-3-methyl-phenol.

To a solution of 4-(4-carboxy-phenyl)-piperidine-1-carboxylic acid tert-butyl ester (2 g, 6.5 mmol) in dry THF (50 mL) is added $BH_3{\cdot}Me_2S$ complex (3.1 mL, 5 eq.) at 0 °C under N_2 (g). The mixture is warmed to room temperature and stirred for 2 hours. The

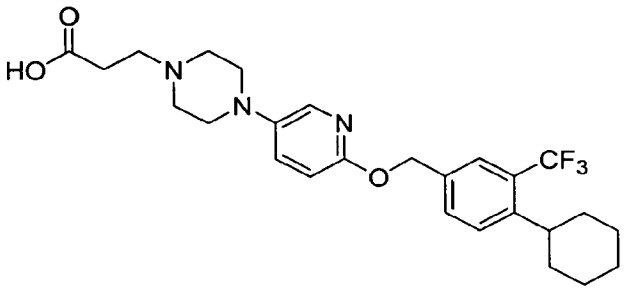
mixture is then heated at 60°C for 15 minutes to complete the reaction. The reaction mixture is cooled in an ice bath and quenched by the slow addition of water (50 mL). The mixture is extracted with EtOAc (3 x 40 mL). The combined organic layers are washed with saturated $NaHCO_3$ (aq), brine, and dried over Na_2SO_4. After concentration, the crude residue, 4-(4-hydroxymethyl-phenyl)-piperidine-1-carboxylic acid tert-butyl ester, is directly used in the next step without further purification.

To a mixture of 4-cyclohexyl-3-methyl-phenol (65 mg, 0.34 mmol, 1 eq.), 4-(4-Hydroxymethyl-phenyl)-piperidine-1-carboxylic acid tert-butyl ester (100 mg, 0.34 mmol, 1 eq.) and PPh_3 (134 mg, 0.51 mmol, 1.5 eq.) in dry DCM (3 mL) is added 1,1'-(azodicarbonyl)-dipipperidine (129 mg, 0.51 mmol, 1.5 eq.) in DCM (1 mL). The mixture is stirred at room temperature for 12 hours. After concentration, the residue is purified by silica gel chromatography (10% EtOAc in hexanes) to give 4-[4-(4-cyclohexyl-3-methyl-phenoxymethyl)-phenyl]-piperidine-1-carboxylic acid tert-butyl ester.

A solution of 4-[4-(4-cyclohexyl-3-methyl-phenoxymethyl)-phenyl]-piperidine-1-carboxylic acid tert-butyl ester (127 mg, 0.27 mmol) in DCM/TFA (1:2 v/v, 3 mL) is stirred for 40 minutes. After concentration, the residue obtained is dissolved in methanol (2 mL). DIEA (130 μL, 1.36 mmol, 5 eq.) and *t*-butyl acrylate (80 μL, 0.54 mmol, 2 eq.) are added to this solution. The reaction mixture is heated at 90°C for 30 minutes using microwave irradiation. After concentration, the residue is purified by silica gel chromatography (40% EtOAc in hexanes) to give 3-{4-[4-(4-cyclohexyl-3-methyl-phenoxymethyl)-phenyl]-piperidin-1-yl}-propionic acid tert-butyl ester. This material is dissolved in DCM/TFA (1:1 v/v, 3 mL), and the solution is stirred at room temperature for 40 minutes. After concentration, the crude product is purified by preparative RP LC-MS to give 3-{4-[4-(4-cyclohexyl-3-methyl-phenoxymethyl)-phenyl]-piperidin-1-yl}-propionic acid: ^{1}H NMR (CD_3OD, 400 MHz) δ 7.41(d, 2H, J = 8 Hz), 7.28 (d, 2H, J = 8 Hz), 7.08(m, 1H), 6.75-6.73 (2H), 5.01 (s, 2H), 3.69 (d, 2H, J = 10 Hz), 3.46 (t, 2H, J = 7 Hz), 3.18(m, 2H), 2.95 m, 1H), 2.86 (t, 2H, J = 7 Hz), 2.65 (m, 1H), 2.27 (s, 3H), 2.18 (m, 2H), 2.04-1.70 (7H), 1.46-1.30 (5H); MS (ES^+): (436.3, $M+1)^+$.

Example 2

3-{4-[6-(4-Cyclohexyl-3-trifluoromethyl-benzyloxy)-pyridin-3-yl]-piperazin-1-yl}-propionic acid



To a solution of 4-chloro-3-(trifluoromethyl)benzyl alcohol (2.87 g, 13.63 mmol) in DMF (40 mL) is added sodium hydride (60% in mineral oil, 654 mg, 16.36 mmol) at 0 °C and the reaction mixture is stirred at 0 °C for 30 minutes. 4-methoxy-benzyl chloride (2.35 g, 15 mmol) in DMF (10 mL) is added and the reaction mixture is stirred at 0 °C for 1 h and at room temperature for 3 hours. The reaction mixture is poured into saturated aqueous NH_4Cl (300 mL) and extracted with EtOAc. The combined extracts are washed with brine (2 × 80 mL) and dried over Na_2SO_4. After concentration, the residue is purified by silica gel chromatography (8:1 hexanes/EtOAc) to give 1-Chloro-4-(4-methoxy-benzyloxymethyl)-2-trifluoromethyl-benzene.

1-Chloro-4-(4-methoxy-benzyloxymethyl)-2-trifluoromethyl-benzene (2 g, 6.51 mmol), $Pd(t\text{-}Bu_3P)_2$ (66.54 mg, 0.13 mmol) and cyclohexylzinc bromide/THF solution (0.5 M, 40 mL, 19.5 mmol) are mixed in 1-methyl-2-pyrrolidinone (NMP) (40 mL). The mixture is purged with N_2 (g) and then heated at 105 °C for 16 hours. The reaction mixture is poured into saturated aqueous NH_4Cl (250 mL) and extracted with EtOAc. The combined extracts are washed with brine and dried over Na_2SO_4. After concentration, the residue is purified by silica gel chromatography (8:1 hexanes/EtOAc) to give 1-Cyclohexyl-4-(4-methoxy-benzyloxymethyl)-2-trifluoromethyl-benzene. To a solution of this material in DCM (8 mL) is added TFA (8 mL). The reaction mixture is stirred at room temperature for 16 hours. After concentration, the residue is partitioned between saturated aqueous NH_4Cl and EtOAc. The aqueous phase is extracted with EtOAc. The combined organic extracts are washed with brine and dried over Na_2SO_4. After concentration, the residue is purified by

silica gel chromatography (4:1 hexanes/EtOAc) to give (4-Cyclohexyl-3-trifluoromethyl-phenyl)-methanol.

To a solution of (4-cyclohexyl-3-trifluoromethyl-phenyl)-methanol (258 mg, 1.0 mmol) in DMF (7 mL) is added sodium hydride (60% in mineral oil, 60 mg, 1.5 mmol) at 0 °C and the reaction mixture is stirred at 0 °C for 30 minutes. After the addition of a solution of 2-chloro-5-bromopyridine (231 mg, 1.2 mmol) in DMF (3 mL), the reaction mixture is stirred at 0 °C for 1 h and at room temperature for 18 hours. The reaction mixture is poured into saturated aqueous NH_4Cl and extracted with EtOAc. The combined extracts are washed with brine and dried over Na_2SO_4. After concentration, the residue is purified by silica gel chromatography (19:1 hexanes/EtOAc) to give 5-Bromo-2-(4-cyclohexyl-3-trifluoromethyl-benzyloxy)-pyridine.

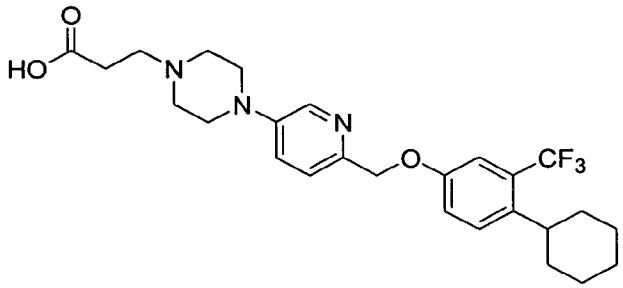
5-Bromo-2-(4-cyclohexyl-3-trifluoromethyl-benzyloxy)-pyridine (332 mg, 0.8 mmol), *tert*-butyl 1-piperazine-carboxylate (178 mg, 0.96 mmol), $Pd(dppf)Cl_2$ (17.5 mg, 0.024 mmol), dppf (20 mg, 0.036 mmol) and sodium *tert*-butoxide (115 mg, 1.19 mmol) are mixed in toluene (2 mL). The mixture is purged with N_2 (g), heated at 80 °C for 14 h, poured into saturated aqueous $NaHCO_3$ and extracted with EtOAc. The combined extracts are washed with brine and dried over Na_2SO_4. After concentration, the residue is purified by silica gel chromatography (180:25:1 hexanes/EtOAc/Et_3N) to give 4-[6-(4-Cyclohexyl-3-trifluoromethyl-benzyloxy)-pyridin-3-yl]-piperazine-1-carboxylic acid tert-butyl ester.

To a solution of 4-[6-(4-Cyclohexyl-3-trifluoromethyl-benzyloxy)-pyridin-3-yl]-piperazine-1-carboxylic acid tert-butyl ester (155 mg, 0.398 mmol) in DCM (2 mL) is added trifluoroacetic acid (TFA) (4 mL). The reaction mixture is stirred at room temperature for 30 minutes and evaporated to dryness. The residue obtained is mixed with *tert*-butyl acrylate (76 mg, 0.6 mmol) and DIEA (193 mg, 1.49 mmol) in MeOH (4 mL) and the mixture is heated in a microwave oven at 90 °C for 30 minutes. The reaction mixture is poured into saturated aqueous $NaHCO_3$ and extracted with EtOAc. The combined extracts are washed with brine and dried over Na_2SO_4. After concentration, the residue is purified by silica gel chromatography (150:50:1 hexanes/EtOAc/Et_3N) to give 3-{4-[6-(4-Cyclohexyl-3-trifluoromethyl-benzyloxy)-pyridin-3-yl]-piperazin-1-yl}-propionic acid tert-butyl ester. This material is dissolved in DCM/TFA (1:1 v/v, 2 mL), and the solution is stirred at room temperature for 1 hour. After concentration, the crude product is purified by preparative RP

LC-MS to give 3-{4-[6-(4-Cyclohexyl-3-trifluoromethyl-benzyloxy)-pyridin-3-yl]-piperazin-1-yl}-propionic acid. ^{1}H NMR (CD_3OD): 1.28-1.85 (10H), 2.88 (t, J = 6.2 Hz, 2H), 2.90 (m, 1H), 3.15-3.85 (8H), 3.69 (t, J = 6.2 Hz, 2H), 5.42 (s, 2H), 7.38 (br, 1H), 7.57 (d, J = 7 Hz, 1H), 7.65 (d, J = 7 Hz, 1H), 7.71 (s, 1H), 7.91 (s, 1H), 8.05 (br, 1H); ESI-MS *m/z* 492.2 (MH^+).

Example 3

3-{4-[6-(4-Cyclohexyl-3-trifluoromethyl-phenoxymethyl)-pyridin-3-yl]-piperazin-1-yl}-propionic acid



2,5-Dibromopyridine (10 mmol), $Pd(Ph_3P)_4$ (0.3 mmol) and zinc cyanate (10 mmol) are mixed in DMF (12 mL) and purged with N_2. The mixture is heated in a microwave reactor at 135 °C for 15 minutes, poured into saturated NH_4Cl solution, and extracted with EtOAc. The combined extracts are washed with saturated aqueous NaCl and dried over Na_2SO_4. After concentration, the residue is purified by silica gel chromatography (9:1 hexanes/EtOAc) to give 5-bromo-pyridine-2-carbonitrile.

5-Bromo-pyridine-2-carbonitrile (8 mmol), *tert*-butyl 1-piperazine-carboxylate (9.6 mmol), $Pd(dppf)Cl_2$ (0.24 mmol), dppf (0.36 mmol) and sodium *tert*-butoxide (11.9 mmol) are mixed in toluene (12 mL) and purged with N_2. The mixture is heated in a microwave reactor at 120 °C for 15 minutes, poured into saturated Na_2CO_3 solution and extracted with EtOAc. The combined extracts are washed with saturated aqueous NaCl and dried over Na_2SO_4. After concentration, the residue is purified by silica gel chromatography (2:1 hexanes/EtOAc) to give *tert*-butyl 4-(6-cyano-pyridin-3-yl)-piperazine-1-carboxylate.

To a solution of *tert*-butyl 4-(6-cyano-pyridin-3-yl)-piperazine-1-carboxylate (2.15 mmol) in THF (20 mL) is added a solution of DIBAL-H in THF (1.0 M, 13 mmol) dropwise

and the reaction mixture is stirred at room temperature for 15 minutes. After it is cooled to 0 °C, the reaction mixture is mixed with a solution of aqueous HCl (2 N, 5 mL) after which the reaction mixture is partitioned between saturated Na_2CO_3 solution and EtOAc. The aqueous phase is extracted with EtOAc. The combined organic extracts are washed with saturated aqueous NaCl and dried over Na_2SO_4. After concentration, the residue is purified by silica gel chromatography (3:7 hexanes/EtOAc) to give *tert*-butyl 4-(6-formyl-pyridin-3-yl)-piperazine-1-carboxylate.

To a solution of *tert*-butyl 4-(6-formyl-pyridin-3-yl)-piperazine-1-carboxylate (0.39 mmol) in THF (10 mL) is added $NaBH_4$ (2.72 mmol) and the reaction mixture is stirred at room temperature for 1 hour. After it is cooled to 0 °C, the reaction mixture is slowly mixed with ice cold water (5 mL) and then partitioned between saturated Na_2CO_3 solution and 10% MeOH in EtOAc. The aqueous phase is extracted with 10% MeOH in EtOAc. The combined organic extracts are washed with saturated aqueous NaCl and dried over Na_2SO_4. After concentration, the residue is purified by silica gel chromatography (100/10/1 EtOAc/MeOH/Et_3N) to give *tert*-butyl 4-(6-hydroxymethyl-pyridin-3-yl)-piperazine-1-carboxylate.

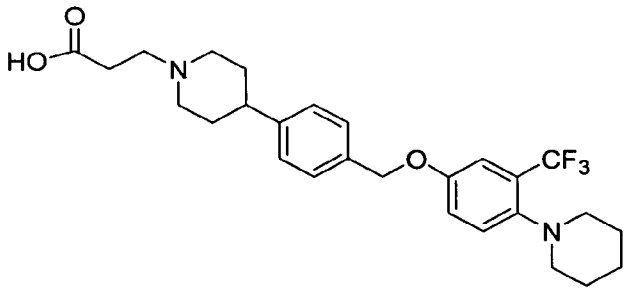
tert-Butyl 4-(6-hydroxymethyl-pyridin-3-yl)-piperazine-1-carboxylate (0.22 mmol), 4-Cyclohexyl-3-trifluoromethyl-phenol (0.22 mmol, synthesized in a similar manner as described in a previous example), 1,1'-azodicarbonyl dipiperdine (0.33 mmol) and Ph_3P (0.33 mmol) are mixed in DCM (2 mL). The reaction mixture is stirred at room temperature for 17 h and then partitioned between saturated Na_2CO_3 solution and EtOAc. The aqueous phase is extracted with EtOAc. The combined organic extracts are washed with saturated aqueous NaCl and dried over Na_2SO_4. After concentration, the residue is purified by silica gel chromatography (6:5 hexanes/EtOAc) to give *tert*-butyl 4-[6-(4-cyclohexyl-3-trifluoromethyl-phenoxymethyl)-pyridin-3-yl]-piperazine-1-carboxylate.

To a solution of *tert*-butyl 4-[6-(4-cyclohexyl-3-trifluoromethyl-phenoxymethyl)-pyridin-3-yl]-piperazine-1-carboxylate (0.021 mmol) in DCM (1 mL) is added trifluoroacetic acid (2 mL). The reaction mixture is stirred at room tempertature for 1 h and evaporated to dryness. The residue is mixed with *tert*-butyl acrylate (0.3 mmol) and DIEA (0.6 mmol) in MeOH (1.5 mL). The mixture is heated in a microwave oven at 90 °C for 30 minutes and evaporated to dryness. To a solution of the residue in DCM (1.5 mL) is added

trifluoroacetic acid (1.5 mL). The reaction mixture is stirred at room tempertature for 1 hour. After concentration, the crude residue is purified by preparative RP LC-MS to give 3-{4-[6-(4-Cyclohexyl-3-trifluoromethyl-phenoxymethyl)-pyridin-3-yl]-piperazin-1-yl}-propionic acid. ^{1}H NMR (400 MHz, CD_3OD) δ 1.18-1.79 (10H), 2.75 (t, J = 11.2 Hz, 1H), 2.80 (t, J = 6.8 Hz, 2H), 3.37-3.78 (8H), 3.43 (t, J = 6.8 Hz, 2H), 5.16 (s, 2H), 7.13 (dd, J = 8.4, 2.8 Hz, 1H), 7.15 (s, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.66 (d, J = 8.8 Hz, 1H), 7.75 (dd, J = 8.8, 2.8 Hz, 1H), 8.30 (s, 1H); ESI-MS m/z 492.2 (MH^+).

Example 4

3-{4-[4-(4-Piperidin-1-yl-3-trifluoromethyl-phenoxymethyl)-phenyl]-piperidin-1-yl}-propionic acid



To a solution of 1-Bromo-4-methoxy-2-trifluoromethyl-benzene (500 mg, 1.961 mmol) in 1,4-dioxane (8 mL) is added sequentially: piperidine (2 eq., 3.921 mmol, 0.41 mL), Pd_2dba_3 (2 mol%, 0.039 mmol, 36 mg), K^{t}OBu (1.5 eq., 2.941 mmol, 330 mg) and 1,3-(Bis(2,6-di-*iso*-propylphenyl)-imidazolium chloride (iPrHCl, 4 mol%, 0.078 mmol, 33 mg). The resulting reaction mixture is heated in a sealed tube at 150°C oil bath for 12 hours. After cooling to room temperature, the reaction mixture is concentrated. The residue obtained is partially purified by silica gel chromatography (9:1 hexanes/EtOAc) to give crude 1-(4-Methoxy-2-trifluoromethyl-phenyl)-piperidine.

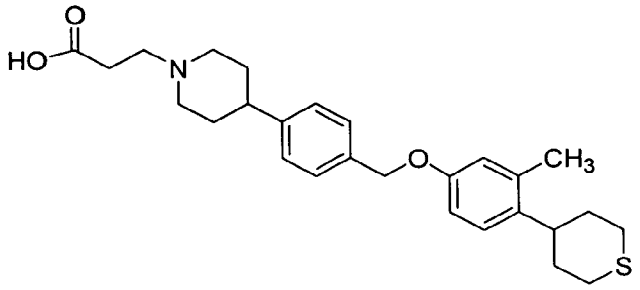
To a solution of crude 1-(4-Methoxy-2-trifluoromethyl-phenyl)-piperidine in dry DCM (3 mL) cooled to -78°C is added BBr_3 (1M in DCM, 3 eq., 1.2 mL). Following this addition, the cooling bath is removed and the reaction is stirred at 25 °C for 12 hours. Upon completion, the reaction is cooled in an ice bath, and water is added dropwise. The quenched reaction is basified to pH=8 by the slow addition of 10 % $NaHCO_3$ (aq). The reaction mixture is diluted with DCM and washed with H_2O followed by saturated aqueous

NaCl. The organic solution is dried over Na_2SO_4. After concentration, the residue is purified by silica gel chromatography (3:1 hexanes/EtOAc) to give 4-Piperidin-1-yl-3-trifluoromethyl-phenol. [MS: (ES^+) 246.1 $(M+1)^+$].

Mitsunobu coupling of 4-(4-Hydroxymethyl-phenyl)-piperidine-1-carboxylic acid tert-butyl ester and 4-Piperidin-1-yl-3-trifluoromethyl-phenol, followed by: Boc deprotection, alkylation with *t*-butyl acrylate, t-butyl ester deprotection, and final RP LC-MS purification as described in a previous example gave 3-{4-[4-(4-Piperidin-1-yl-3-trifluoromethyl-phenoxymethyl)-phenyl]-piperidin-1-yl}-propionic acid as a tan solid. ^1H NMR (DMSO-d_6, 400 MHz) δ 10.25 (bs, 1H), 7.49(d, 1H), 7.41 (d, 2H), 7.27 (d, 2H), 7.30-7.20 (m, 2H), 5.10 (s, 2H), 3.61-3.52 (m, 2H), 3.36-3.26 (m, 2H), 3.14-3.02 (m, 2H), 2.90-2.80 (m, 3H), 2.78-2.72 (m, 4H), 2.03-1.94 (m, 4H), 1.65-1.55 (m, 4H), 1.53-1.45 (m, 2H); MS (ES^+): (491.2, $M+1)^+$.

Example 5

3-(4-{4-[3-Methyl-4-(tetrahydro-thiopyran-4-yl)-phenoxymethyl]-phenyl}-piperidin-1-yl)-propionic acid



Mitsunobu coupling of 4-Bromo-3-methyl-phenol and 4-(4-Hydroxymethyl-phenyl)-piperidine-1-carboxylic acid tert-butyl ester as described in a previous example gave 4-[4-(4-Bromo-3-methyl-phenoxymethyl)-phenyl]-piperidine-1-carboxylic acid tert-butyl ester.

To a solution of 4-[4-(4-Bromo-3-methyl-phenoxymethyl)-phenyl]-piperidine-1-carboxylic acid tert-butyl ester (409 mg, 0.8884 mmol) in dry THF (5 mL) cooled to -78 °C is added n-BuLi (1.6 M in hexanes, 1.1 eq., 0.9772 mmol, 0.61 mL). The resulting mixture

is stirred at -78 °C for 30 minutes and a solution of tetrahydro-thiopyran-4-one (1.1 eq., 0.9772 mmol, 114 mg) in dry THF (0.5 mL) is then added dropwise. After 30 minutes, the reaction mixture is quenched with saturated aqueous NH_4Cl and warmed to room temperature. The reaction mixture is diluted with EtOAc and washed sequentially with H_2O and saturated aqueous NaCl. The organic solution is dried over Na_2SO_4. After concentration, the residue is partially purified by silica gel chromatography (3:1 hexanes/EtOAc) to give crude 4-{4-[4-(4-Hydroxy-tetrahydro-thiopyran-4-yl)-3-methyl-phenoxymethyl]-phenyl}-piperidine-1-carboxylic acid tert-butyl ester.

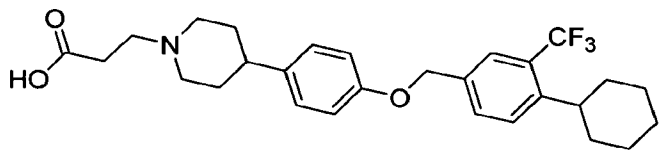
To a solution of crude 4-{4-[4-(4-Hydroxy-tetrahydro-thiopyran-4-yl)-3-methyl-phenoxymethyl]-phenyl}-piperidine-1-carboxylic acid tert-butyl ester in dry DCM (7 mL) is added triethyl silane (4.442 mmol, 517 mg, 0.71 mL) followed by TFA (7 mL). The resulting mixture is stirred at room temperature for 2 hours. After concentration, the crude residue, 4-{4-[3-Methyl-4-(tetrahydro-thiopyran-4-yl)-phenoxymethyl]-phenyl}-piperidine, is directly used in the next step without further purification.

Crude 4-{4-[3-Methyl-4-(tetrahydro-thiopyran-4-yl)-phenoxymethyl]-phenyl}-piperidine is dissolved in MeOH (8 mL) and treated with *t*-butyl acrylate (1.777 mmol, 228 mg, 0.26 mL) and DIEA (4.442 mmol, 574 mg, 0.77 mL). The resulting mixture is heated at 60 °C for 45 minutes. After concentration, the residue is partially purified by silica gel chromatography (0 to 10% MeOH in DCM) to give crude 3-(4-{4-[3-Methyl-4-(tetrahydro-thiopyran-4-yl)-phenoxymethyl]-phenyl}-piperidin-1-yl)-propionic acid tert-butyl ester.

To a solution of crude 3-(4-{4-[3-Methyl-4-(tetrahydro-thiopyran-4-yl)-phenoxymethyl]-phenyl}-piperidin-1-yl)-propionic acid tert-butyl ester in dry DCM (7 mL) is added triethyl silane (5 eq., 4.442 mmol, 517 mg, 0.71 mL) followed by TFA (7 mL). The resulting mixture is stirred at room temperature for 1 hour. After concentration, the crude product is purified by preparative RP LC-MS to give 3-(4-{4-[3-Methyl-4-(tetrahydro-thiopyran-4-yl)-phenoxymethyl]-phenyl}-piperidin-1-yl)-propionic acid as a tan solid. ^1H NMR (DMSO-d_6, 400 MHz) δ 7.44-7.38 (m, 2H), 7.30-7.21 (m, 2H), 7.13-7.05 (m, 1H), 6.83-6.72 (m, 2H), 5.02 (s, 2H), 3.61-3.52 (m, 2H), 3.15-3.05 (m, 2H), 2.89-2.75 (m, 5H), 2.72-2.60 (m, 3H), 2.33-2.20 (m, 3H), 2.06-1.88 (m, 6H), 1.77-1.61 (m, 1H); MS (ES^+): $(454.2, M+1)^+$.

Example 6

3-{4-[4-(4-Cyclohexyl-3-trifluoromethyl-benzyloxy)-phenyl]-piperidin-1-yl}-propionic acid



To a solution of 4-(4-hydroxy-phenyl)-piperidine-1-carboxylic acid tert-butyl ester (1 eq) in anhydrous DMF is added NaH (1.1 eq) at room temperature. After 5 minutes, 1-chloro-4-chloromethyl-2-trifluoromethyl-benzene (1.1 eq) in DMF is added. The resulting mixture is stirred for 30 minutes. After aqueous work up, flash column chromatography (10% EtOAc/hexane) gave 4-[4-(4-Chloro-3-trifluoromethyl-benzyloxy)-phenyl]-piperidine-1-carboxylic acid tert-butyl ester. [MS: (ES^+) 490.3 $(M+1)^+$].

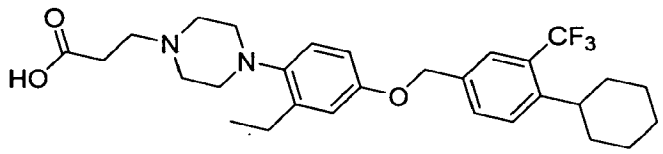
4-[4-(4-Chloro-3-trifluoromethyl-benzyloxy)-phenyl]-piperidine-1-carboxylic acid tert-butyl ester (1 eq) is dissolved in 10% TFA/DCM and stirred for 30 minutes. After concentration, the residue is re-dissolved in DCM and washed with saturated $NaHCO_3$ and brine. The organic layer is dried over Na_2SO_4 and concentrated. The residue is then dissolved in MeOH and *t*-butyl acrylate (2 eq) is added. The resulting solution is heated at 90 ^0C in microwave for 10 minutes. After concentration, purification by flash column chromatography (80% EtOAc/hexane) gave 3-{4-[4-(4-Chloro-3-trifluoromethyl-benzyloxy)-phenyl]-piperidin-1-yl}-propionic acid tert-butyl ester. [MS: (ES^+) 498.2 $(M+1)^+$].

3-{4-[4-(4-Chloro-3-trifluoromethyl-benzyloxy)-phenyl]-piperidin-1-yl}-propionic acid tert-butyl ester (1 eq) and Pd catalyst (0.05 eq) are treated with cyclohxyl zinc bromide in THF. The resulting mixture is heated at 100 ^0C in microwave for 25 minutes. It is then diluted with EtOAc and washed with 1 N HCl. After concentration, purification by flash column chromatography (EtOAc) gave 3-{4-[4-(4-Cyclohexyl-3-trifluoromethyl-benzyloxy)-phenyl]-piperidin-1-yl}-propionic acid tert-butyl ester. [MS: (ES^+) 546.3 $(M+1)^+$].

3-{4-[4-(4-Cyclohexyl-3-trifluoromethyl-benzyloxy)-phenyl]-piperidin-1-yl}-propionic acid tert-butyl ester is dissolved in DCM and treated with TFA (50% v/v). After 2 h at room temperature, it is concentrated to give a residue which is purified by RP LC-MS to give 3-{4-[4-(4-Cyclohexyl-3-trifluoromethyl-benzyloxy)-phenyl]-piperidin-1-yl}-propionic acid. ^{1}HNMR (400 MHz, CD_3OD) δ 7.83 (1H, s), 7.65 (1H, d), 7.55 (1H, d), 7.20 (4H, m), 5.45 (2H, s), 3.66 (2H, d), 3.44 (2H, m), 3.20 (2H, m), 2.81 (2H, m), 2.68 (2H, m), 1.84 (9H, m), 1.36 (5H, m). MS (ES^+): 490.3 $(M+1)^+$.

Example 7

3-{4-[4-(4-Cyclohexyl-3-trifluoromethyl-benzyloxy)-2-ethyl-phenyl]-piperazin-1-yl}-propionic acid



1-Bromo-2-ethyl-4-methoxy-benzene (1 eq), piperazine-1-carboxylic acid tert-butyl ester (1.5 eq), $Pd(OAc)_2$ (0.03 eq), phosphine ligand (0.06 eq), sodium *t*-butoxide (1.7 eq) are mixed in toluene and the resulting mixture is heated at 120 ^{0}C in microwave for 20 minutes. It is then diluted with EtOAc/hexane and filtered through celite. Flash column chromatography (20% EtOAc/hexane) gave 4-(2-Ethyl-4-methoxy-phenyl)-piperazine-1-carboxylic acid tert-butyl ester. MS: (ES^+): 321.2 $(M+1)^+$.

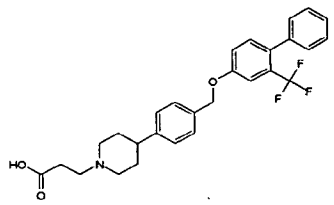
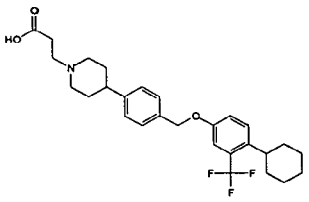
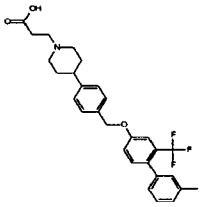
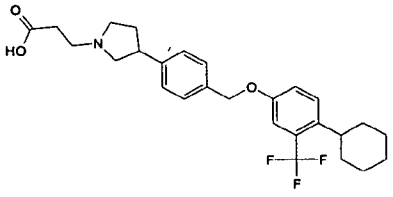
4-(2-Ethyl-4-methoxy-phenyl)-piperazine-1-carboxylic acid tert-butyl ester is refluxed in 48% HBr for 2 hours. After concentration, the residue is dissolved in DCM and $(Boc)_2O$ (1.5 eq) and triethylamine (4 eq) are added. The resulting mixture is stirred at room temperature for 30 minutes. After aqueous workup, flash column chromatography (30% EtOAc/hexane) gave 4-(2-Ethyl-4-hydroxy-phenyl)-piperazine-1-carboxylic acid tert-butyl ester. MS: (ES^+): 307.2 $(M+1)^+$.

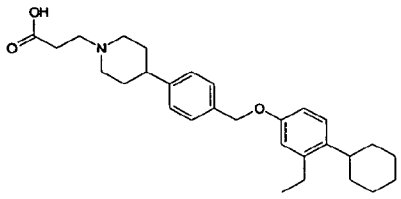
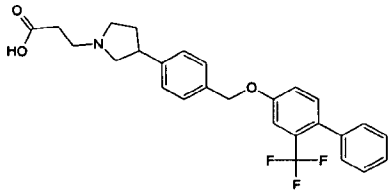
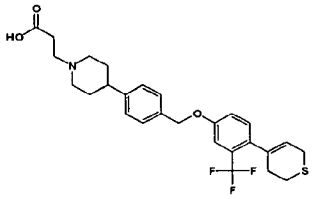
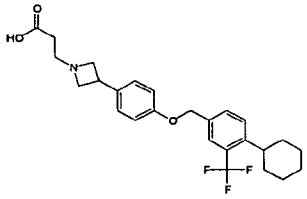
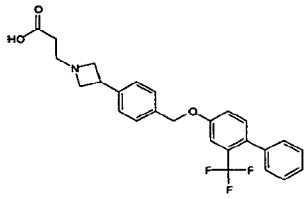
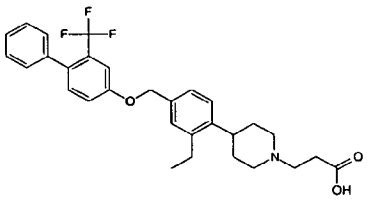
3-{4-[4-(4-Cyclohexyl-3-trifluoromethyl-benzyloxy)-2-ethyl-phenyl]-piperazin-1-yl}-propionic acid is synthesized similarly based on Scheme 1. ^{1}HNMR (400 MHz, CD_3OD)

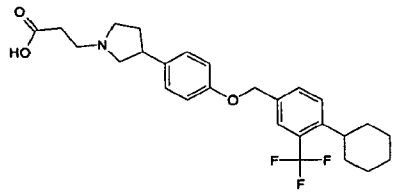
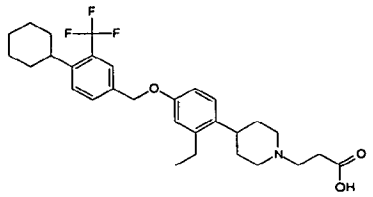
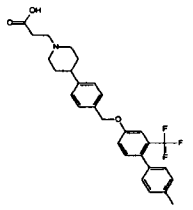
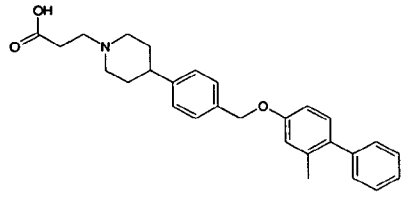
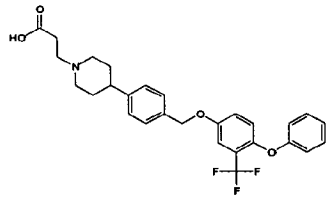
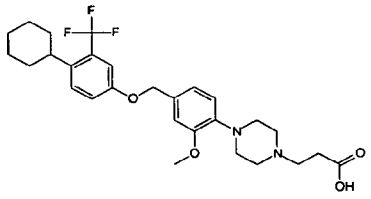
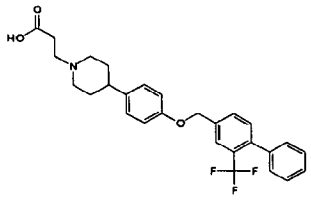
δ 7.75 (1H, s), 7.66 (1H, d), 7.55 (1H, d), 7.21 (1H, m), 6.93 (2H, m), 5.10 (2H, s), 3.30 (10H, m), 2.94 (2H, m), 2.75 (2H, m), 1.80 (5H, m), 1.40 (8H, m). MS (ES^+): 519.3 $(M+1)^+$.

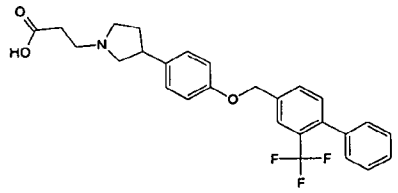
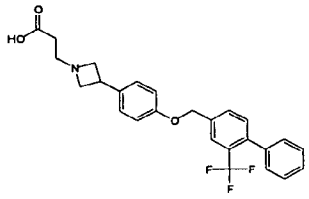
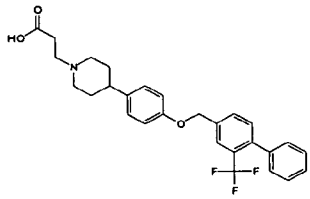
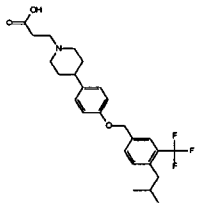
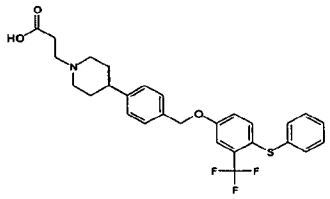
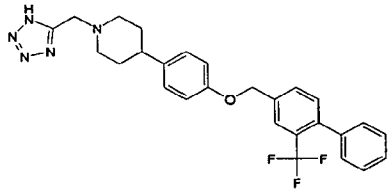
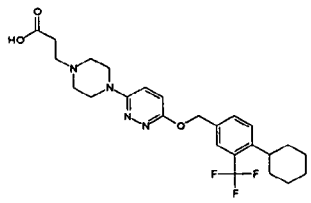
By repeating the procedure described in the above examples, using appropriate starting materials, the following compounds of Formula I are obtained as identified in Table 1.

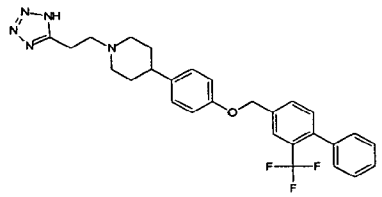
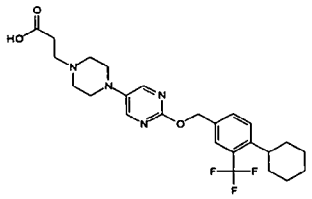
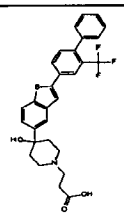
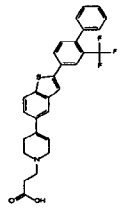
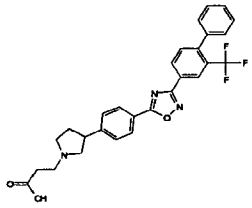
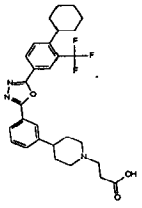
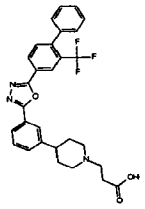
TABLE 1

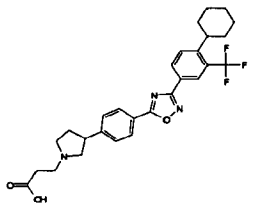
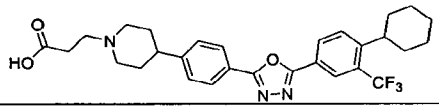
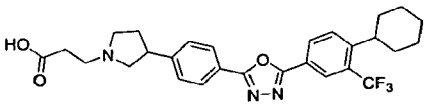
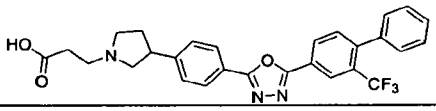
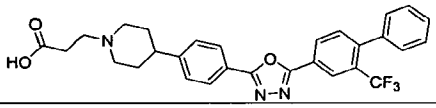
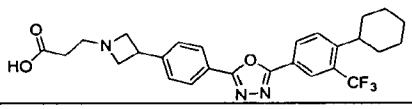
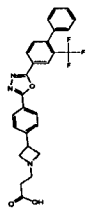
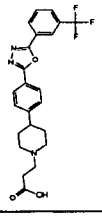
Example	Structure	Physical Data MS ES (M+1)
8		484.5
9		490.6
10		498.5
11		476.5

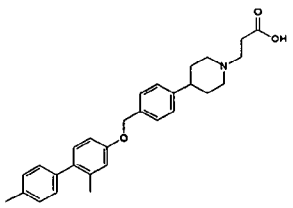
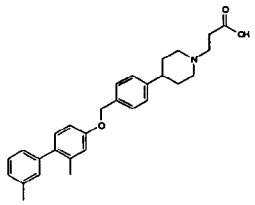
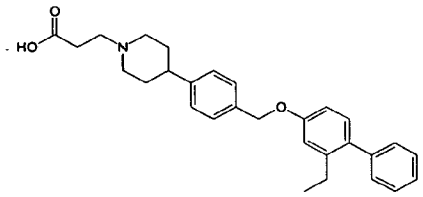
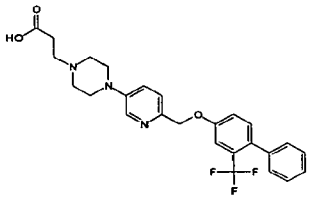
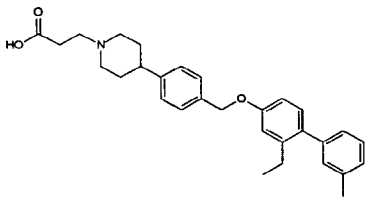
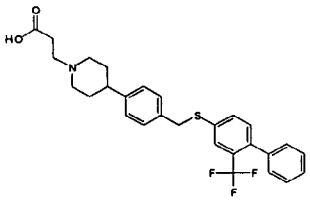
Example	Structure	Physical Data MS ES (M+1)
12		450.6
13		470.5
14		506.6
15		462.5
16		456.5
17		512.6

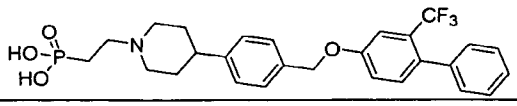
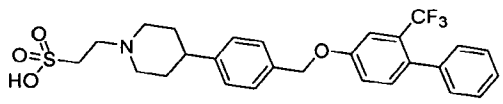
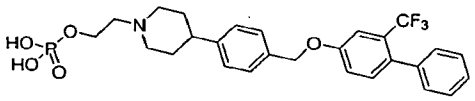
Example	Structure	Physical Data MS ES (M+1)
18		476.5
19		518.6
20		498.5
21		430.6
22		500.5
23		521.6
24		484.5

Example	Structure	Physical Data MS ES (M+1)
25		470.5
26		456.5
27		484.5
28		464.5
29		516.6
30		494.5
31		493.5

Example	Structure	Physical Data MS ES (M+1)
32		508.6
33		493.5
34		526.6
35		508.6
36		508.5
37		528.6
38		522.5

Example	Structure	Physical Data MS ES (M+1)
39		514.6
40		528.6
41		514.6
42		508.5
43		522.5
44		500.5
45		494.5
46		446.4

Example	Structure	Physical Data MS ES (M+1)
47		444.6
48		444.6
49		444.3
50		486.2
51		458.3
52		500.2

Example	Structure	Physical Data MS ES (M+1)
53		
54		
55		

Example 56

Compounds of Formula I Exhibit Biological Activity

A. In vitro: A scintillation proximity assay (SPA) for measuring GTP [γ-^{35}S] binding to membranes prepared from CHO cells expressing human EDG/S1P receptors

EDG-1 (S1P1) GTP [γ-^{35}S] binding assay: Membrane protein suspensions are prepared from CHO cell clones stably expressing a human EDG-1 N-terminal c-myc tag. Solutions of test compounds ranging from 10mM to 0.01nM are prepared in DMSO/50mM HCl and then diluted into assay buffer (20mM HEPES, pH7.4, 100mM NaCl, 10mM MgCl2, 0.1% fat free BSA). Assay buffer containing 10mM GDP is mixed with wheat germ agglutinin-coated SPA-beads (1mg/well) followed by the addition of human EDG-1 membrane protein suspension (10 μg/well) and test compound. The bead/membrane/compound assay components are then mixed for 10-15 minutes on a shaker at room temperature. GTP [γ-^{35}S] (200pM) and bead/membrane/compound assay mixture are added to individual wells of a 96 well Optiplate ™ (final volume 225 μl/well), sealed and incubated at room temperature for 110 to 120 minutes under constant shaking. After centrifugation (2000rpm, 10 minutes) luminescence is measured with a TopCount ™ instrument.

EC50 values are obtained by fitting the GTP [γ-^{35}S] binding curves (raw data) with the dose response curve-fitting tool of ORIGIN V. 6.1. Basal binding (no compound) and the highest stimulation of GTP [γ-^{35}S] binding achieved by an agonist are used as the fitting range. Seven different concentrations are used to generate a concentration response curve (using two or three data points per concentration).

EDG-3,-5,-6 and -8 GTP [γ-^{35}S] binding assays are carried out in a comparable manner to the EDG-1 GTP [[γ-^{35}S] binding assay using membranes from CHO, or in the case of EDG-8 RH7777 membranes, from cells stably expressing c-terminal c-myc tagged or untagged receptors. Concentrations of EDG receptor expressing membranes range between 13-19 μg per well. Compounds of the invention were tested according to the above assay and were observed to exhibit selectivity for the EDG-1 receptor. For example, example 1 has an EC_{50} of 0.22 nM in the above assay and is at least 1000 fold selective for EDG-1 compared to one or more of the other receptors including EDG-3, EDG-5, EDG-6 and EDG-8.

B. <u>In vitro: FLIPR calcium flux assay</u>

Compounds of the invention are tested for agonist activity on EDG-1, EDG-3, EDG-5, and EDG-6 with a FLIPR calcium flux assay. Briefly, CHO cells expressing an EDG receptor are maintained in F-12K medium (ATCC), containing 5% FBS, with 500ug/ml of G418. Prior to the assay, the cells are plated in 384 black clear bottom plates at the density of 10,000 cells/well/25μl in the medium of F-12K containing 1% FBS. The second day, the cells are washed three times (25 μl/each) with washing buffer. About 25 μl of dye are added to each well and incubated for 1 hour at 37°C and 5% CO_2. The cells are then washed four times with washing buffer (25 μl/each). The calcium flux is assayed after adding 25 μl of SEQ2871 solution to each well of cells. The same assay is performed with cells expressing each of the different EDG receptors. Titration in the FLIPR calcium flux assay is recorded over a 3-minute interval, and quantitated as maximal peak height percentage response relative to EDG-1 activation.

C. In vivo: Screening Assays for measurement of blood lymphocyte depletion and assessment of heart effect

Measurement of circulating lymphocytes: Compounds are dissolved in DMSO and diluted to obtain a final concentration of 4% DMSO (v/v, final concentration) and then further diluted in a constant volume of Tween80 25%/H2O, v/v. Tween80 25%/H2O (200 µl), 4% DMSO, and FTY720 (10µg) are included as negative and positive controls, respectively. Mice (C57bl/6 male, 6-10 week-old) are administered 250-300 µL of compound solution orally by gavages under short isoflurane anesthesia.

Blood is collected from the retro-orbital sinus 6 and 24 hours after drug administration under short isoflurane anesthesia. Whole blood samples are subjected to hematology analysis. Peripheral lymphocyte counts are determined using an automated analyzer. Subpopulations of peripheral blood lymphocytes are stained by fluorochrome-conjugated specific antibodies and analyzed using a fluorescent activating cell sorter (Facscalibur). Two mice are used to assess the lymphocyte depletion activity of each compound screened. The result is an ED_{50}, which is defined as the effective dose required displaying 50 % of blood lymphocyte depletion. Compounds of the invention were tested according to the above assay and were preferably found to exhibit an ED_{50} of less than 1mg/kg, more preferably an ED_{50} of less than 0.5 mg/kg. For example, compound 1 exhibits an ED50 of 0.1 mg/kg.

Assessment of Heart Effect: The effects of compounds on cardiac function are monitored using the AnonyMOUSE ECG screening system. Electrocardiograms are recorded in conscious mice (C57bl/6 male, 6-10 week-old) before and after compound administration. ECG signals are then processed and analyzed using the e-MOUSE software. 90 µg of compound further diluted in 200µl water, 15% DMSO are injected IP. Four mice are used to assess the heart effect of each compound.

D: In vivo: Anti-angiogenic Activity

Porous chambers containing (i) sphingosine-1-phosphate (5 µM/chamber) or (ii) human VEGF (1 µg/chamber) in 0.5 ml of 0.8% w/v agar (containing heparin, 20 U/ml) are implanted subcutaneously in the flank of mice. S1P or VEGF induces the growth of

vascularized tissue around the chamber. This response is dose-dependent and can be quantified by measuring the weight and blood content of the tissue. Mice are treated once a day orally or intravenously with a compound of formula I starting 4-6 hours before implantation of the chambers and continuing for 4 days. The animals are sacrificed for measurement of the vascularized tissues 24 hours after the last dose. The weight and blood content of the vascularized tissues around the chamber is determined. Animals treated with a compound of formula I show reduced weight and/or blood content of the vascularized tissues compared to animals treated with vehicle alone. Compounds of Formula I are anti-angiogenic when administered at a dose of about 0.3 to about 3mg/kg.

E: <u>In vitro: Antitumor Activity</u>

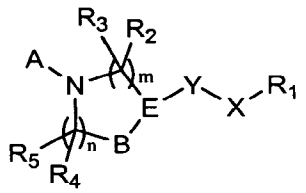
A mouse breast cancer cell line originally isolated from mammary carcinomas is used, e.g. JygMC(A). The cell number is adjusted to $5x10^5$ for plating in fresh medium before the procedure. Cells are incubated with fresh medium containing 2.5mM of thymidine without FCS for 12 hours and then washed twice with PBS, followed by addition of fresh medium with 10% FCS and additionally incubated for another 12 hours. Thereafter the cells are incubated with fresh medium containing 2.5mM of thymidine without FCS for 12 hours. To release the cells from the block, the cells are washed twice with PBS and replated in fresh medium with 10% FCS. After synchronization, the cells are incubated with or without various concentrations of a compound of formula I for 3, 6, 9, 12, 18 or 24 hours. The cells are harvested after treatment with 0.2% EDTA, fixed with ice-cold 70% ethanol solution, hydrolyzed with 250□g/ml of RNaseA (type 1-A: Sigma Chem. Co.) at 37°C for 30 minutes and stained with propidium iodide at 10mg/ml for 20 minutes. After the incubation period, the number of cells is determined both by counting cells in a Coulter counter and by the SRB colorimetric assay. Under these conditions compounds of formula I inhibit the proliferation of the tumor cells at concentrations ranging from 10^{-12} to 10^{-6} M.

It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and understanding of this application and scope of the appended claims. All publications,

patents, and patent applications cited herein are hereby incorporated by reference for all purposes.

WE CLAIM

1. A compound of Formula I:



in which:

n is chosen from 0, 1 and 2; m is chosen from 1, 2 and 3;

R_1 is chosen from C_{6-10}aryl and C_{5-10}heteroaryl; wherein any aryl or heteroaryl of R_1 is optionally substituted by a radical chosen from $C_{6-10}arylC_{0-4}$alkyl, $C_{5-6}heteroarylC_{0-4}$alkyl, $C_{3-8}cycloalkylC_{0-4}$alkyl, $C_{3-8}heterocycloalkylC_{0-4}$alkyl or C_{1-10}alkyl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl group of R_1 can be optionally substituted by 1 to 5 radicals chosen from halo, C_{1-10}alkyl, C_{1-10}alkoxy, halo-substituted-C_{1-10}alkyl and halo-substituted-C_{1-10}alkoxy; and any alkyl group of R_1 can optionally have a methylene replaced by an atom or group chosen from –S–, –S(O)–, –$S(O)_2$–, –NR_7– and –O–; wherein R_7 is chosen from hydrogen and C_{1-6}alkyl;

R_2, R_3, R_4 and R_5 are independently chosen from hydrogen, halo, hydroxy, C_{1-10}alkyl, C_{1-10}alkoxy, halo-substituted-C_{1-10}alkyl and halo-substituted-C_{1-10}alkoxy;

A is chosen from –$X_1C(O)OR_7$, –$X_1OP(O)(OR_7)_2$, –$X_1P(O)(OR_7)_2$, –$X_1P(O)OR_7$, –$X_1S(O)_2OR_7$, –$X_1P(O)(R_7)OR_7$ and 1*H*-tetrazol-5-yl; wherein X_1 is chosen from a bond, C_{1-3}alkylene and C_{2-3}alkenylene and R_7 is chosen from hydrogen and C_{1-6}alkyl;

B is CR_8R_9; wherein R_8 and R_9 are independently chosen from hydrogen, hydroxy, C_{1-10}alkyl, C_{1-10}alkoxy, halo-substituted-C_{1-10}alkyl and halo-substituted-C_{1-10}alkoxy;

E is chosen from CR_8 or N; wherein R_8 is chosen from hydrogen, hydroxy, C_{1-10}alkyl, C_{1-10}alkoxy, halo-substituted-C_{1-10}alkyl and halo-substituted-C_{1-10}alkoxy; or B is CR_9 and E is carbon and B and E are connected via a double bond;

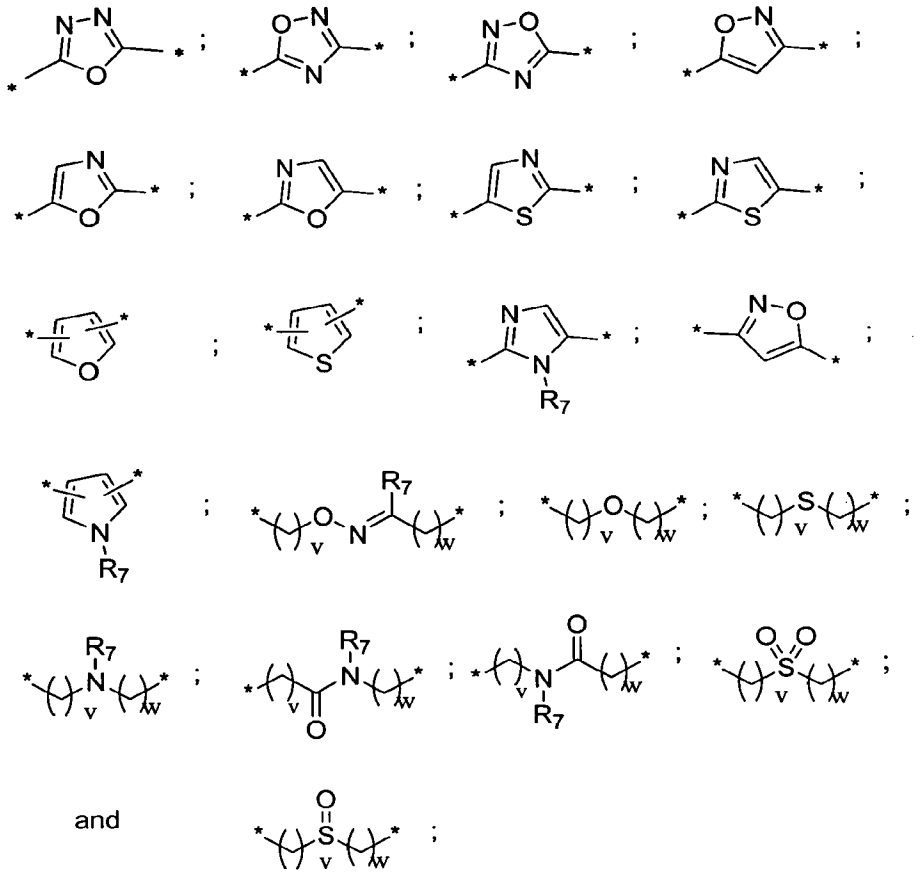
X is a bond or is chosen from $-X_1OX_2-$, $-X_1NR_7X_2-$, $-X_1C(O)NR_7X_2-$, $-X_1NR_7C(O)X_2-$, $-X_1S(O)X_2-$, $-X_1S(O)_2X_2-$, $-X_1SX_2-$, C_{4-6}heteroarylene and $-X_1ON=C(R_7)X_2-$; wherein X_1 and X_2 are independently chosen from a bond, C_{1-3}alkylene and C_{2-3}alkenylene; R_7 is chosen from hydrogen and C_{1-6}alkyl; and any heteroarylene of X is optionally substituted by a member of the group chosen from halo and C_{1-6}alkyl;

Y is chosen from C_{6-10}aryl and C_{5-10}heteroaryl, wherein any aryl or heteroaryl of Y can be optionally substituted with 1 to 3 radicals chosen from halo, hydoxy, nitro, C_{1-10}alkyl, C_{1-10}alkoxy, halo-substituted C_{1-10}alkyl and halo-substituted C_{1-10}alkoxy; and the pharmaceutically acceptable salts, hydrates, solvates, isomers and prodrugs thereof.

2. The compound of claim 1 in which R_1 is chosen from phenyl, naphthyl and thiophenyl optionally substituted by C_{6-10}arylC_{0-4}alkyl, C_{5-6}heteroarylC_{0-4}alkyl, C_{3-8}cycloalkylC_{0-4}alkyl, C_{3-8}heterocycloalkylC_{0-4}alkyl or C_{1-10}alkyl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl group of R_1 can be optionally substituted by 1 to 5 radicals chosen from halo, C_{1-10}alkyl, C_{1-10}alkoxy, halo-substituted-C_{1-10}alkyl and halo-substituted-C_{1-10}alkoxy; and any alkyl group of R_1 can optionally have a methylene replaced by an atom or group chosen from –S–, –S(O)–, $-S(O)_2-$, $-NR_7-$ and –O–; wherein R_7 is hydrogen or C_{1-6}alkyl.

3. The compound of claim 1 in which A is chosen from $-X_1C(O)OR_7$ and 1*H*-tetrazol-5-yl; wherein X_1 is chosen from a bond, C_{1-3}alkylene and C_{2-3}alkenylene and R_7 is chosen from hydrogen and C_{1-6}alkyl.

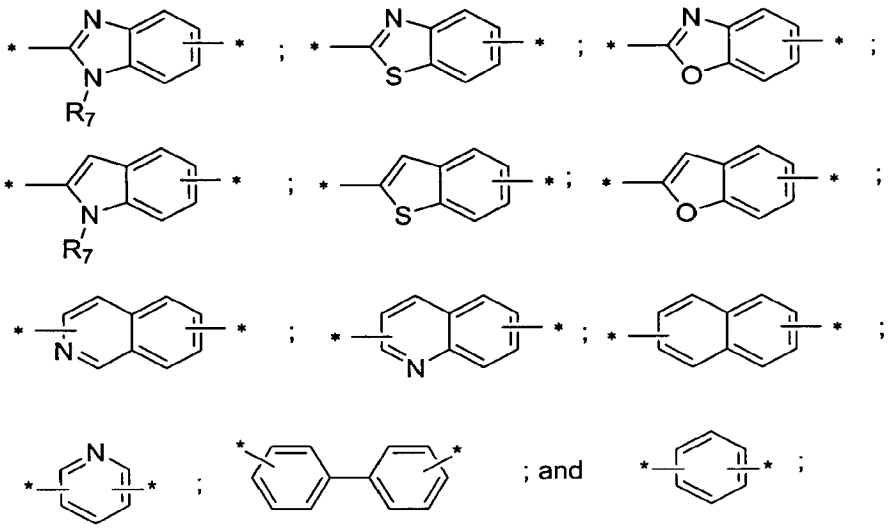
4. The compound of claim 1 in which X is chosen from:



and

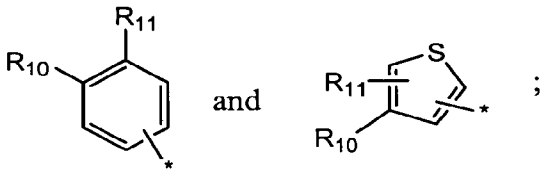
wherein the left and right asterisks of X indicate the point of attachment between R_1 and Y of Formula I, respectively; R_7 is chosen from hydrogen and C_{1-6}alkyl; v and w are independently 0, 1, 2 or 3.

5. The compound of claim 1 in which Y is chosen from:



wherein R_7 is hydrogen or C_{1-6}alkyl; and the left and right asterisks of Y indicate the point of attachment between X and E of Formula I, respectively.

6. The compound of claim 2 in which R_1 is chosen from:



wherein the asterisk is the point of attachment of R_1 with X; R_{10} is C_{6-10}arylC_{0-4}alkyl, C_{5-6}heteroarylC_{0-4}alkyl, C_{3-8}cycloalkylC_{0-4}alkyl, C_{3-8}heterocycloalkylC_{0-4}alkyl or C_{1-10}alkyl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl group of R_{10} can be optionally substituted by 1 to 3 radicals chosen from halo, C_{1-10}alkyl, C_{1-10}alkoxy, halo-substituted-C_{1-10}alkyl and halo-substituted-C_{1-10}alkoxy; and any alkyl group of R_{10} can optionally have a methylene replaced by an atom or group chosen from –S–, –S(O)–, –$S(O)_2$–, –NR_7– and –O–; wherein R_7 is hydrogen or C_{1-6}alkyl; and R_{11} is selected from halo, C_{1-10}alkyl, C_{1-10}alkoxy, halo-substituted-C_{1-10}alkyl and halo-substituted-C_{1-10}alkoxy.

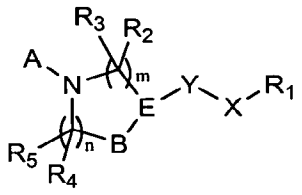
7. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1 in combination with a pharmaceutically acceptable excipient.

8. A method for treating a disease in an animal in which alteration of EDG/S1P receptor mediated signal transduction can prevent, inhibit or ameliorate the pathology and/or symptomology of the disease, which method comprises administering to the animal a therapeutically effective amount of a compound of Claim 1.

9. A method for preventing or treating disorders or diseases mediated by lymphocytes, for preventing or treating acute or chronic transplant rejection or T-cell mediated inflammatory or autoimmune diseases, for inhibiting or controlling deregulated angiogenesis, or for preventing or treating diseases mediated by a neo-angiogenesis process or associated with deregulated angiogenesis in a subject comprising administering to the subject in need thereof an effective amount of a compound of claims1, or a pharmaceutically acceptable salt thereof.

10. The use of a compound of claim 1 in the manufacture of a medicament for treating a disease in an animal in which alteration of EDG/S1P receptor mediated signal transduction contributes to the pathology and/or symptomology of the disease.

11. A process for preparing a compound of Formula I:



in which:

n is chosen from 0, 1 and 2; m is chosen from 1, 2 and 3;

R_1 is chosen from C_{6-10}aryl and C_{5-10}heteroaryl; wherein any aryl or heteroaryl of R_1 is optionally substituted by a radical chosen from C_{6-10}arylC_{0-4}alkyl, C_{5-6}heteroarylC_{0-4}alkyl, C_{3-8}cycloalkylC_{0-4}alkyl, C_{3-8}heterocycloalkylC_{0-4}alkyl or C_{1-10}alkyl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl group of R_1 can be optionally substituted by 1 to 5 radicals chosen from halo, C_{1-10}alkyl, C_{1-10}alkoxy, halo-substituted-C_{1-10}alkyl and halo-

substituted-C_{1-10}alkoxy; and any alkyl group of R_1 can optionally have a methylene replaced by an atom or group chosen from –S–, –S(O)–, –$S(O)_2$–, –NR_7– and –O–; wherein R_7 is chosen from hydrogen and C_{1-6}alkyl;

R_2, R_3, R_4 and R_5 are independently chosen from hydrogen, halo, hydroxy, C_{1-10}alkyl, C_{1-10}alkoxy, halo-substituted-C_{1-10}alkyl and halo-substituted-C_{1-10}alkoxy;

A is chosen from –$X_1C(O)OR_7$, –$X_1OP(O)(OR_7)_2$, –$X_1P(O)(OR_7)_2$, –$X_1P(O)OR_7$, –$X_1S(O)_2OR_7$, –$X_1P(O)(R_7)OR_7$ and 1*H*-tetrazol-5-yl; wherein X_1 is chosen from a bond, C_{1-3}alkylene and C_{2-3}alkenylene and R_7 is chosen from hydrogen and C_{1-6}alkyl;

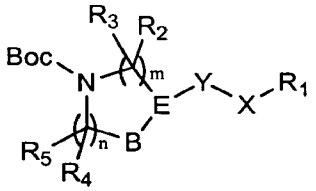
B is CR_8R_9; wherein R_8 and R_9 are independently chosen from hydrogen, hydroxy, C_{1-10}alkyl, C_{1-10}alkoxy, halo-substituted-C_{1-10}alkyl and halo-substituted-C_{1-10}alkoxy;

E is chosen from CR_8 or N; wherein R_8 is chosen from hydrogen, hydroxy, C_{1-10}alkyl, C_{1-10}alkoxy, halo-substituted-C_{1-10}alkyl and halo-substituted-C_{1-10}alkoxy; or B is CR_9 and E is carbon and B and E are connected via a double bond;

X is a bond or is chosen from –X_1OX_2–, –$X_1NR_7X_2$–, –$X_1C(O)NR_7X_2$–, –$X_1NR_7C(O)X_2$–, –$X_1S(O)X_2$–, –$X_1S(O)_2X_2$–, –X_1SX_2–, C_{4-6}heteroarylene and –$X_1ON{=}C(R_7)X_2$–; wherein X_1 and X_2 are independently chosen from a bond, C_{1-3}alkylene and C_{2-3}alkenylene; R_7 is chosen from hydrogen and C_{1-6}alkyl; and any heteroarylene of X is optionally substituted by a member of the group chosen from halo and C_{1-6}alkyl;

Y is chosen from C_{6-10}aryl and C_{5-10}heteroaryl, wherein any aryl or heteroaryl of Y can be optionally substituted with 1 to 3 radicals chosen from halo, hydoxy, nitro, C_{1-10}alkyl, C_{1-10}alkoxy, halo-substituted C_{1-10}alkyl and halo-substituted C_{1-10}alkoxy; which process comprises:

(a) reacting a compound of formula 2:



(2)

with either *t*-butyl acrylate, acylonitrile/NaN_3 or bromoacetonitrile/NaN_3; wherein B, E, Y, X, R_1 R_2, R_3, R_4 and R_5 are as described above; and

(b) optionally converting a compound of the invention into a pharmaceutically acceptable salt;

(c) optionally converting a salt form of a compound of the invention to a non-salt form;

(d) optionally converting an unoxidized form of a compound of the invention into a pharmaceutically acceptable N-oxide;

(e) optionally converting an N-oxide form of a compound of the invention to its unoxidized form;

(f) optionally resolving an individual isomer of a compound of the invention from a mixture of isomers;

(g) optionally converting a non-derivatized compound of the invention into a pharmaceutically acceptable prodrug derivative; and

(h) optionally converting a prodrug derivative of a compound of the invention to its non-derivatized form.

IMMUNOSUPPRESSANT COMPOUNDS AND COMPOSITIONS

ABSTRACT OF THE DISCLOSURE

The present invention relates to immunosuppressant, process for their production, their uses and pharmaceutical compositions containing them. The invention provides a novel class of compounds useful in the treatment or prevention of diseases or disorders mediated by lymphocyte interactions, particularly diseases associated with EDG receptor mediated signal transduction.